ADASUVE™ (*Staccato* Loxapine)

Edwin Kamemoto, PhD
Executive Director, Regulatory Affairs
Alexza Pharmaceuticals

Proposed Indication

ADASUVE is an orally inhaled loxapine product indicated for:

the acute treatment of agitation associated with Schizophrenia or Bipolar I Disorder in adults

Agenda

Introduction	***James Cassella, PhD* (Moderator)** Sr. VP, Research & Development Alexza Pharmaceuticals
Agitation and Treatment	***Scott Zeller, MD*** *Chief, Psychiatric Emergency Services* *Alameda County Medical Center, Oakland, CA*
ADASUVE: Drug-Device Combination Product	***James Cassella, PhD***
Efficacy Review	***James Cassella, PhD***
Clinical Safety Review	***Robert Fishman, MD, FCCP*** VP, Clinical Development Alexza Pharmaceuticals
Risk Management Plans	***James Cassella, PhD***
Closing Remarks	***Leslie Zun, MD, MBA*** *Chair, Department of Emergency Medicine* *Mount Sinai Hospital Chicago*

Experts Involved with the Program

- James Donohue, MD, FCCP
  - Professor of Medicine and Chief, Pulmonary Diseases Division, University of North Carolina School of Medicine
  - Member, Board of Directors, American Thoracic Society
  - Editorial Board, Journal of COPD
  - Independent expert reviewer for 004-104 (lung safety study in normal healthy volunteers)
- Leon S. Greos, MD, FAAAAI, FACAAI
  - Clinical Assistant Professor, University of Colorado School of Pharmacy
  - Past-President, Clinical Research Network / Allergy and Respiratory, LLC
  - Practicing Physician, Colorado Allergy & Asthma Centers, PC
  - PI for 004-105 study (asthma)
- Michael Lesem, MD
  - Medical Director, Claghorn-Lesem Research Clinic
  - PI for 004-201, 004-301, 004-302 studies
- Gary Slatko, MD
  - Chief Medical Officer, Paragon Rx
  - REMS Advisor

Other Experts

- **Nicholas J Gross MD, PhD, FRCP, FCCP**
  - Attending physician, St. Francis Hospital, Hartford and University of Connecticut School of Medicine
  - Formerly, Professor of Medicine and of Molecular Biochemistry, Stritch-Loyola Medical School
- **Jeffrey Finman, PhD**
  - Jupiter Point Pharma Consulting LLC
  - Consulting Statistician
- **Scott Zeller, MD**
  - Chief, Psychiatric Emergency Services, Alameda County Medical Center, Oakland, CA
  - President of American Association for Emergency Psychiatry
- **Leslie Zun, MD, MBA**
  - Chair, Department of Emergency Medicine, Mount Sinai Hospital Chicago
  - Professor and Chair, Department of Emergency Medicine, Chicago Medical School

ADASUVE Introduction

James Cassella, PhD
Senior VP, Research & Development
Alexza Pharmaceuticals

Agitation and Treatment

Scott Zeller, MD
Chief, Psychiatric Emergency Services
Alameda County Medical Center, Oakland, CA

President
American Association for Emergency Psychiatry

Agitation

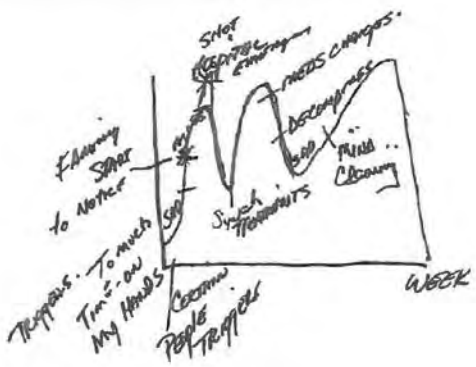
- Defined as “Excessive Verbal and/or Motor Activity” [1]
- Not a disease itself, but commonly associated with many CNS / psychiatric conditions
  - 2.4 million adults with schizophrenia in US [2]
  - 5.7 million adults with bipolar disorder [2]
- Agitation estimated to involve ~1.7 million psychiatric emergencies per year [3]
  - Not discussed nearly enough relative to its prevalence

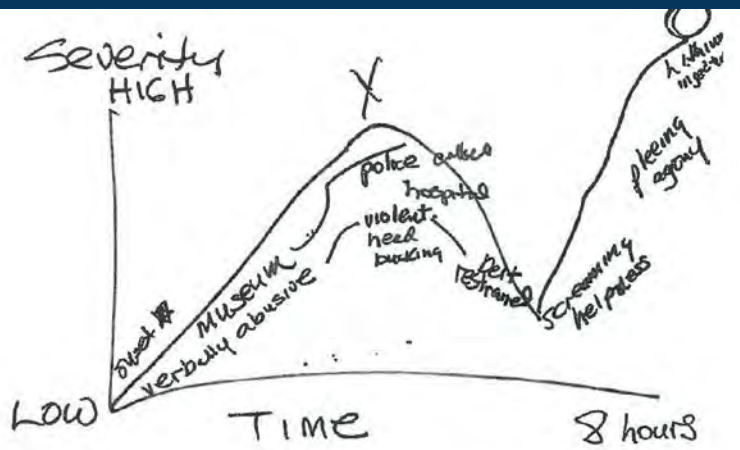
1. Citrome, L. *Postgrad Med*. 2002 Dec;112(6):85-8, 94-6.
2. National Institutes of Mental Health, US Census
3. Sachs GS. *Journal Clinical Psych*. 2006;67(10):5-12

Patients with Agitation Describe Their Experience as:

- Explosive, angry
- Low frustration tolerance
- Anxious
- Feel they are losing control
- Uncontrollable
- Overwhelmed, restless
- Verbally abusive
- Aggressive, violent, wanting to fight
- Paranoia

Patients with Agitation Know what is Happening to Them





Patients' Response to Treatments

- Want to avoid a bad treatment experience [1]
- Don't want to be coerced [1]
- Prefer non-invasive treatment and want to be part of the treatment decision [1]

1. Allen, M. et al. *J Psychiatr Practice*. 2003; 9(1):39-58.

Safety Risks of Agitation

- Agitation can escalate unpredictably [1, 2]
  - Studies show agitation was present in 30%- 82% cases prior to violent incidents by psychiatric patients [3-9]
- Agitation often precedes violence to others and self
  - 1/5 of patient self-harm requires medical treatment [10]
- 2/3 of staff injuries involving agitated patients occur during containment procedures [11]
  - 8 staff assaults / year in psychiatric emergency services [12]
  - Most result in staff injury severe enough to miss work

1. Citrome L. *Emergency Psychiatry: Principles & Practice.* 2008. 137-147.
2. Bruch S, Zeller S. *Emergency Psychiatry: Principles & Practice.* 2008. 117-124.
3. Owen C, et al. *Psychiatr Serv*.1998;49:1452-1457.
4. Powell G, et al. *Br J Psychiatry*.1994;165:107-112.
5. Sheridan M, et al. *Hosp Community Psychiatry*.1990;41:776-780.
6. Whittington R, et al. *J Psychiatr Ment Health Nurs*.1996;3:47-54.
7. Aiken GJ. *Med Sci Law*. 1984;24:199-207.
8. Lee HK, et al. *Hosp Community Psychiatry*.1989;40:1295-1297.
9. Crowner ML, et al. *Psychiatr Q*. 2005;76:243-256.
10. Foster C, et al. *J Adv Nurs*. 2007;58(2), 140-149.
11. Carmel H, Hunter M. *Hosp Community Psychiatry.* 1989;40:41-46.
12. Currier GW, Allen MH. *Psychiatr Serv,* 2000;51:717-719.

Clinicians' Treatment Goals

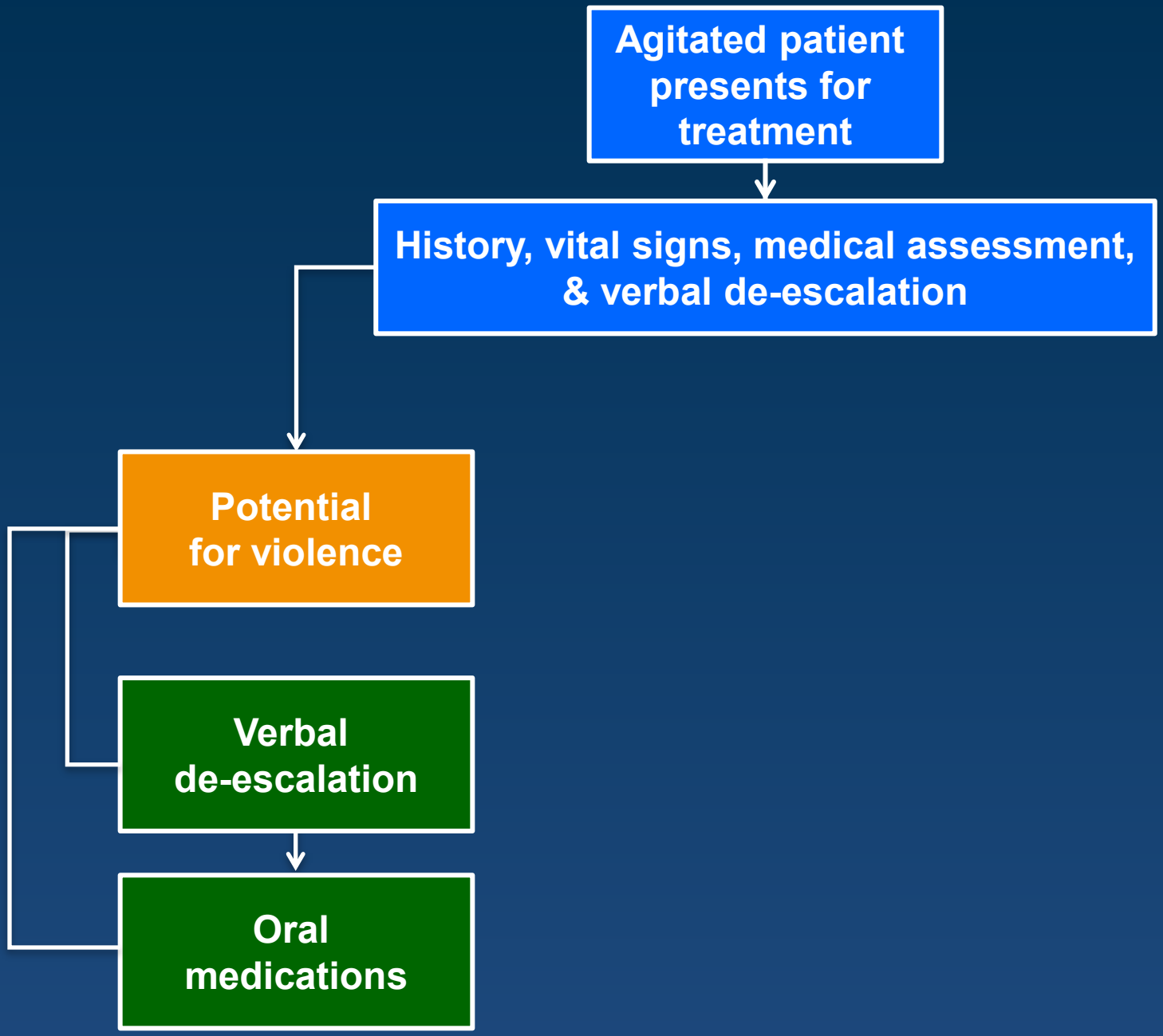
In Emergency Psychiatry [1]

- Rapidly stabilize acute crisis
- Avoid coercion
- Use least restrictive alternative
- Build / maintain therapeutic alliance
- Disposition appropriately

In Treating Agitation [2, 3]

- Reduce anguish, dangerous behaviors promptly
- Intervene prior to violence
- Positive treatment experience

1. Zeller S. *Primary Psychiatry.* 2010;17(6):35-41
2. Allen MH, et al. *J Psychiatr Prac.* 2005;11(suppl 1):1-108.
3. BETA Verbal De-escalation. *W J Emergency Med.* in press Feb 2012



1. Citrome L. *Emergency Psychiatry: Principles & Practice.* 2008. 137-147.
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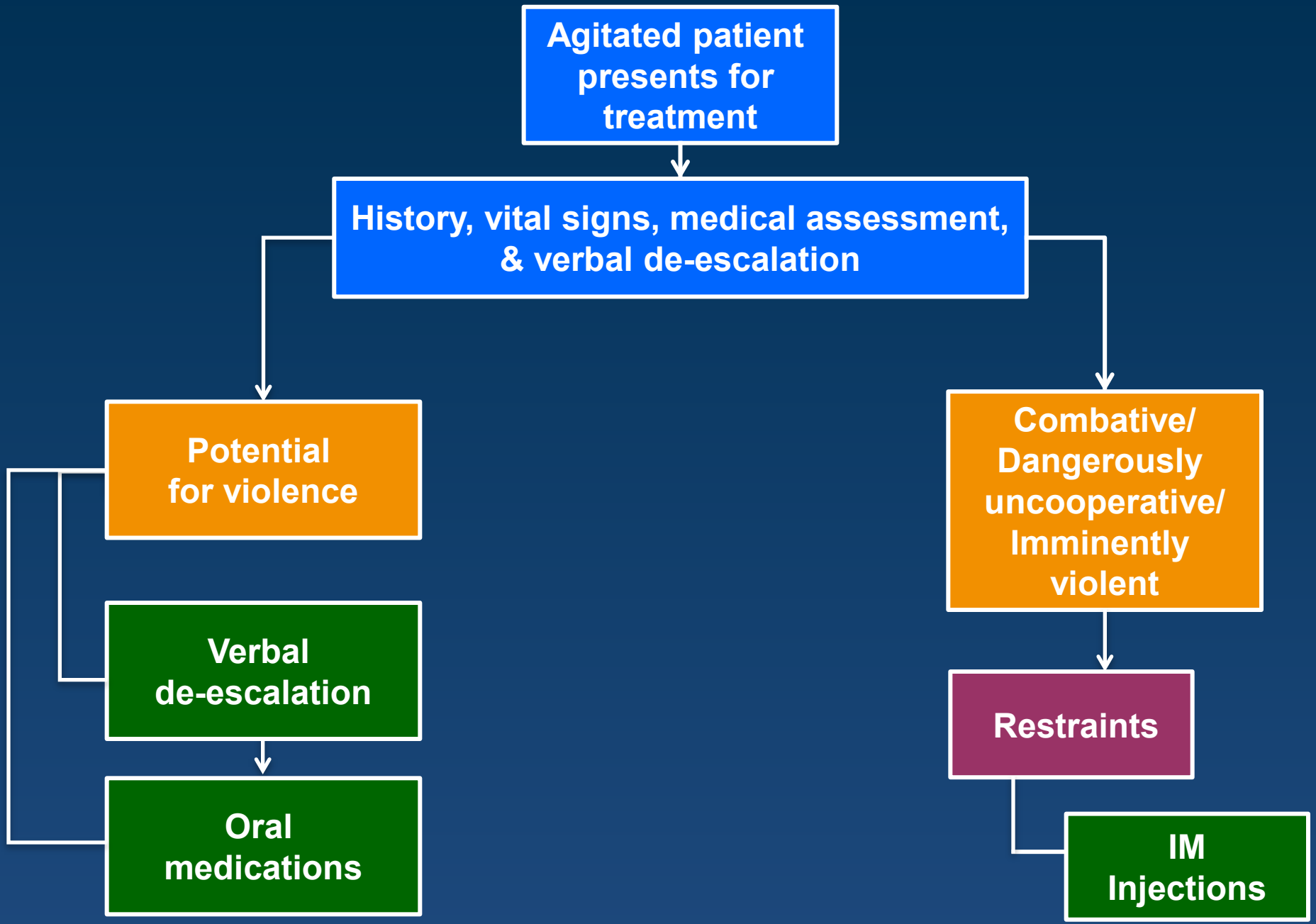

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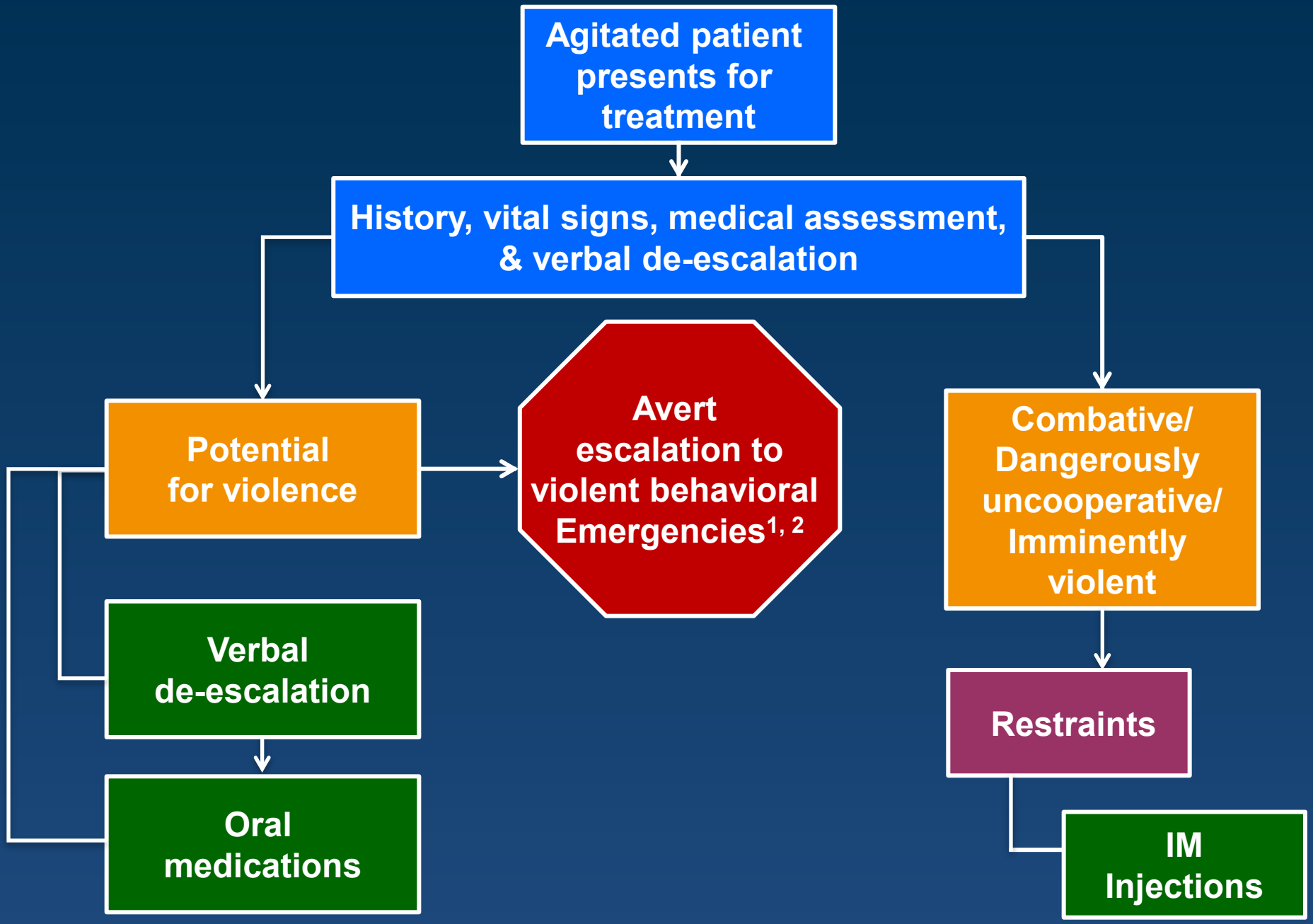

1. Citrome L. *Emergency Psychiatry: Principles & Practice.* 2008. 137-147.
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Current Pharmacologic Agitation Treatment Options

Formulation	Rationale / Use
Oral	• For cooperative patients • Slower onset than injection • Collaborative option
Injection (patient restrained or in restraints)	• Generally coercive • Can be avoided in most cases • Invasive, painful and unpleasant for patients • Conflicts with Least Restrictive Alternative policy / law and JCAHO/CMS, patient advocacy

The Centers for Medicare and Medicaid Services (CMS) Conditions of Participation for Hospitals

- "Seclusion and restraint may be used only when less restrictive interventions have been determined to be ineffective to protect the patient, a staff member or others from harm."
- "All patients have the right to be free from restraint or seclusion, of any form, imposed as a means of coercion, discipline, convenience or retaliation by staff."

Source: 2006 Federal Register 482.13; 71426-8

National Association of State Mental Health Program Directors (NASMHPD)

- "Every episode of restraint or seclusion is harmful to the individual..."
- "Public scrutiny of restraint and seclusion is increasing and legal standards are changing, consistent with growing evidence that the use of these interventions is inherently dangerous, arbitrary, and generally avoidable."

Source: Haimowitz S et. al., NASMHPD, October 2006

Current Pharmacologic Agitation Treatment Options

Formulation	Rationale / Use	Medication Options	Dose
Oral	• For cooperative patients • Slower onset than injection • Collaborative option	haloperidol	5 mg IM / PO
		olanzapine	10 mg IM 10-20 mg PO
		ziprasidone	10-20 mg IM 40 – 160 mg PO
		aripiprazole	9.75 mg IM
Injection (patient restrained or in restraints)	• Generally coercive • Can be avoided in most cases • Invasive, painful and unpleasant for patients • Conflicts with Least Restrictive Alternative policy / law and JCAHO/CMS, patient advocacy	lorazepam	2 mg IM 0.5 – 2 mg PO
		midazolam	5 – 15 mg IM

The Current Agitation Treatment Gap

We Have IMs:

- Invasive
- Coercive
- Relatively rapid

Or Orals

- Non-invasive
- Non-coercive
- Relatively slow

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What We Don't Have:

- Rapid treatment

And

- Non-invasive, non-coercive, and collaborative
- Relieve patients' distress and improve long term treatment outcomes

The Ideal Agitation Treatment

- **Expert Consensus Guideline Series on Treatment of Behavioral Emergencies [1] (AAEP)**
  - **"Control of aggressive behavior emerged as the highest priority during the emergency; however; preserving the physician-patient relationship was rated a close second and became a top-priority in the long term."**
  - **"The experts consider speed of onset and reliability of delivery the two most important factors to consider in choosing a route of administration; they also consider patient preference quite important."**

1. Allen MH, et al. *J Psychiatr Prac.* 2005;11(suppl 1):1-108.

ADASUVE: A Drug-Device Combination Product

James Cassella, PhD

Loxapine

- Introduced more than 35 years ago in US for the treatment of schizophrenia and exacerbation of psychotic symptoms
- Well-established efficacy and safety profile
  - Antipsychotic effects similar to first generation antipsychotics (eg, haloperidol)
    - Mid-potency dopamine D2 blocker
  - Some clinical effects consistent with atypical antipsychotics (eg, clozapine, olanzapine)
    - High-potency blockade at 5HT-2_A receptor

Receptor	D1	D2	5HT-2_A	α1	α2	H1
Loxapine K_i (nM)	18	9.8	2	28	250	5

Staccato is a Unique Inhalation System

- Not like a metered dose inhaler or dry powder inhaler
  - No excipients
  - No priming
  - No hand/breath coordination
  - No forceful inhalation required
  - Aerosol simply entrained in patient's inhalation
- *Staccato* designed for systemic delivery

The *Staccato* System

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- Single-use drug delivery product for treatment of acute and intermittent conditions
- Ideally suited to meet patient's need for rapid onset of therapeutic effect

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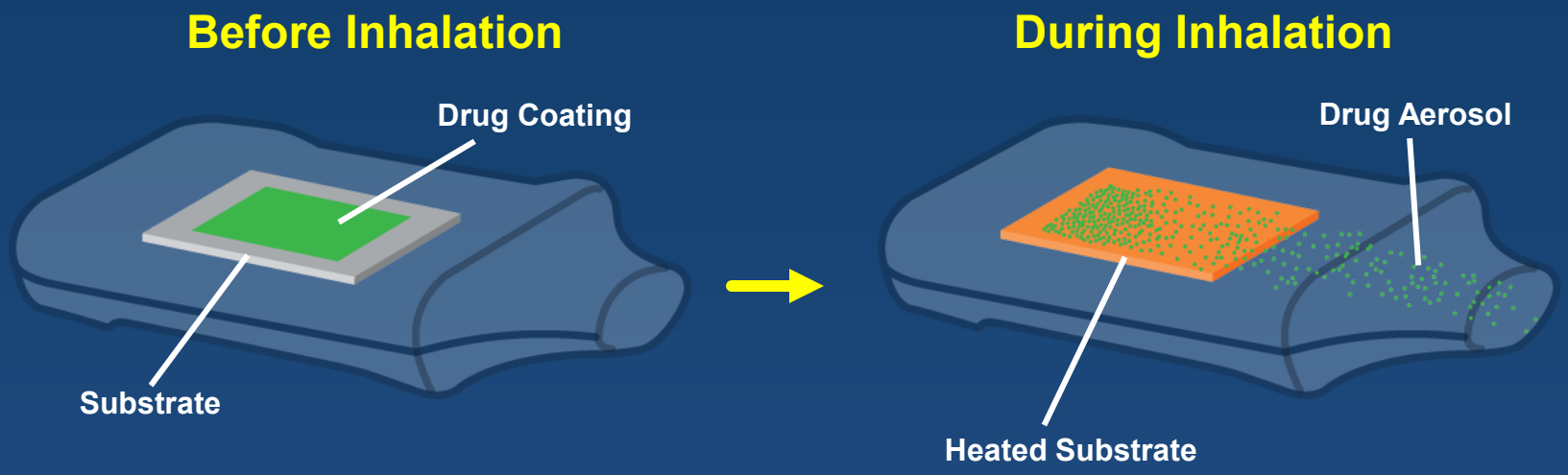
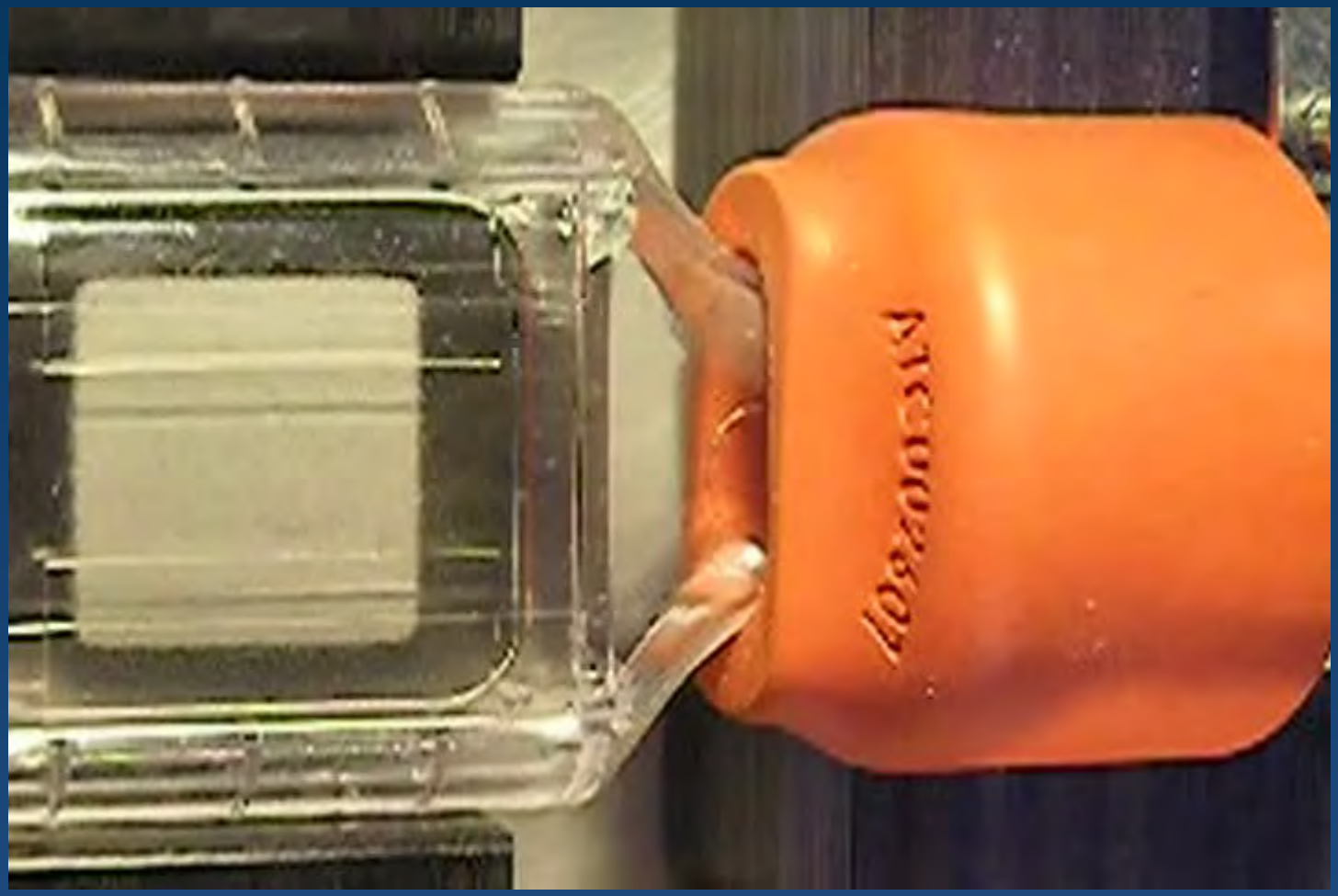
- Transformation of excipient-free drug into a thermal condensation aerosol for delivery to the lung for systemic action



Staccato Aerosolization



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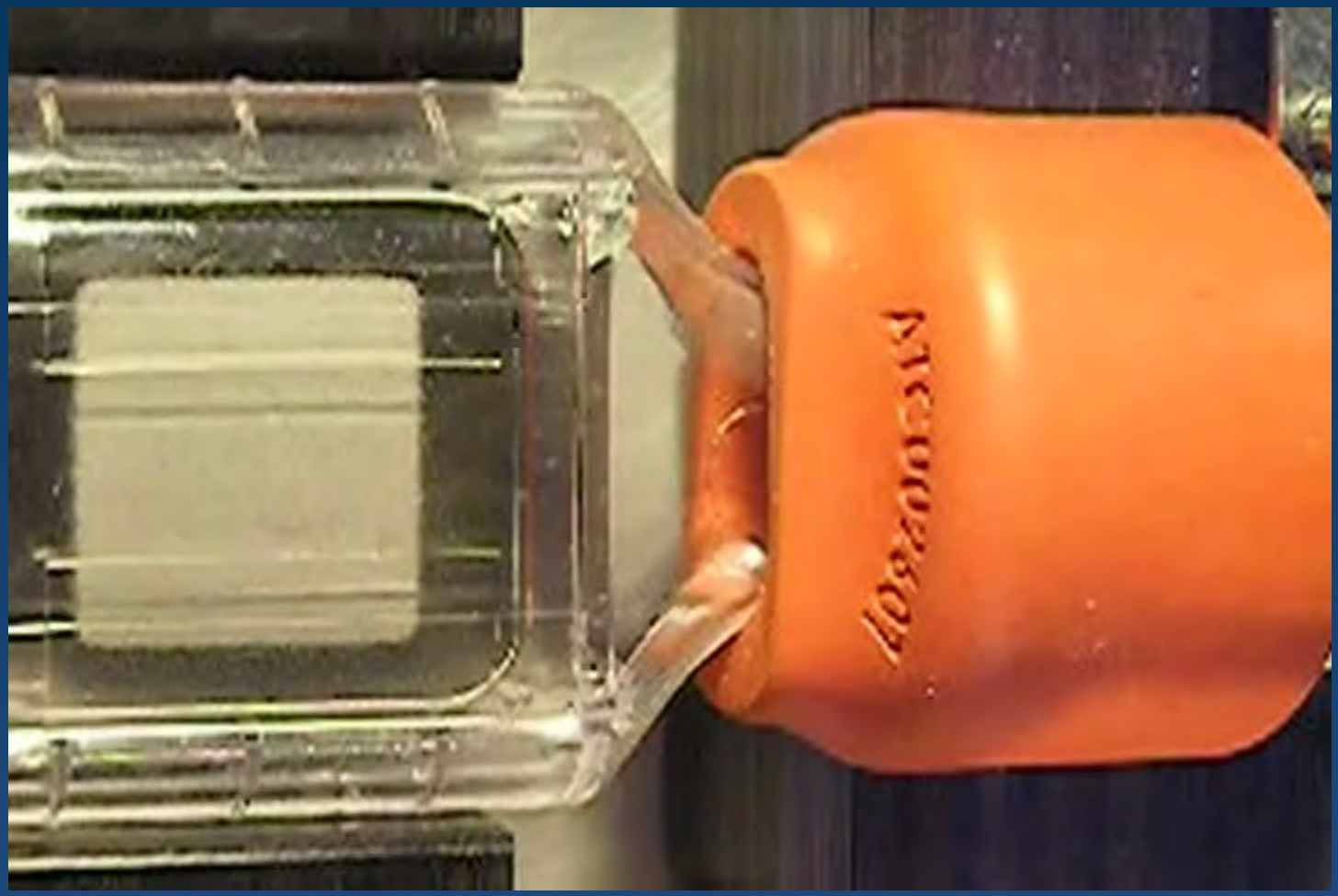

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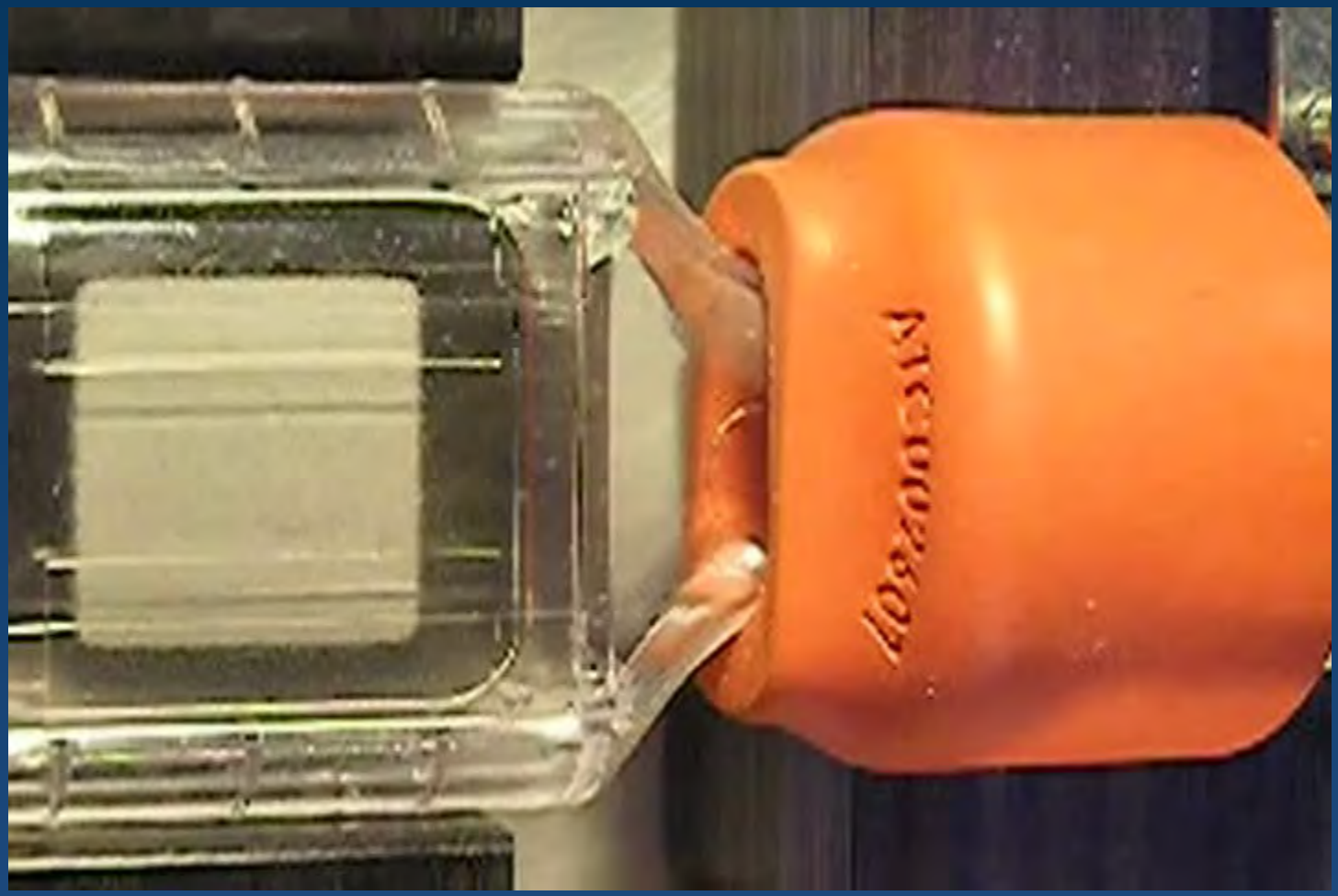
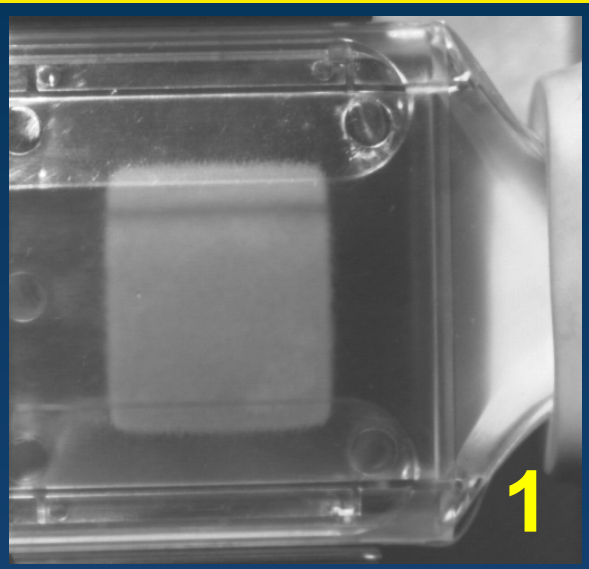


http://aerosol.alexza.com/

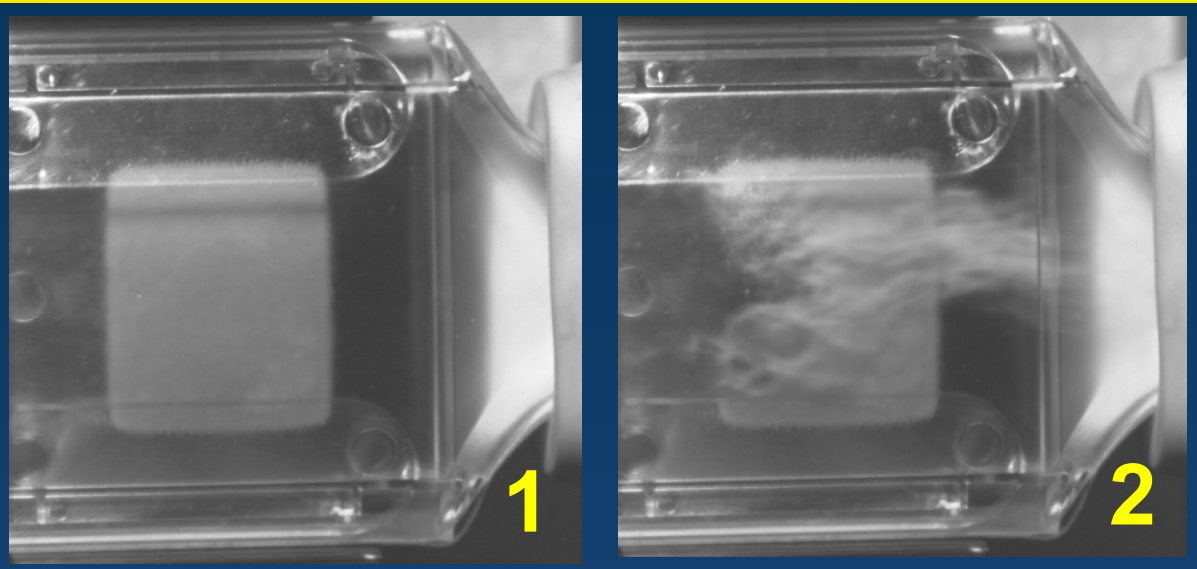
Time Course of Vaporization

Time = 0
actuation
of heating



Time Course of Vaporization

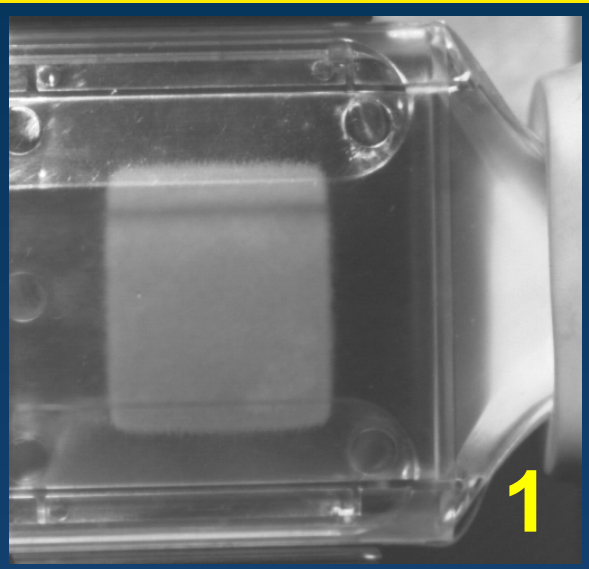
Time = 0 actuation of heating

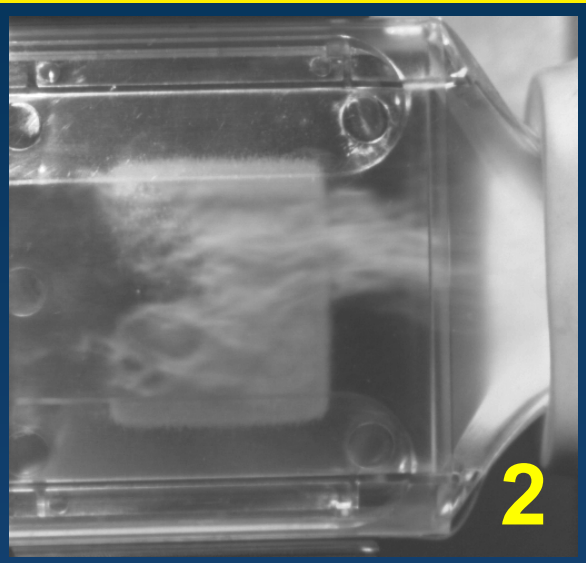


Time = 30 ms

Time Course of Vaporization

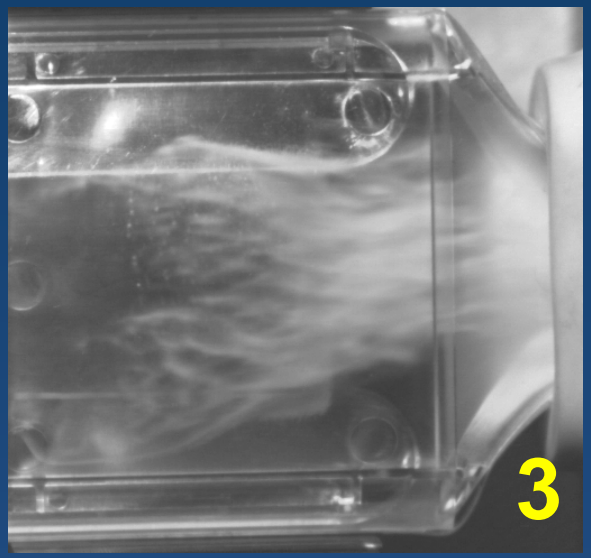
Time = 0 actuation of heating





Time = 30 ms

Time = 50 ms



Time Course of Vaporization

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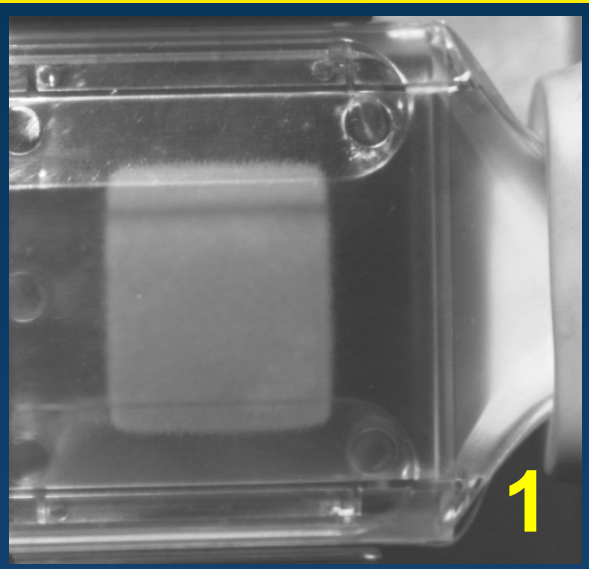

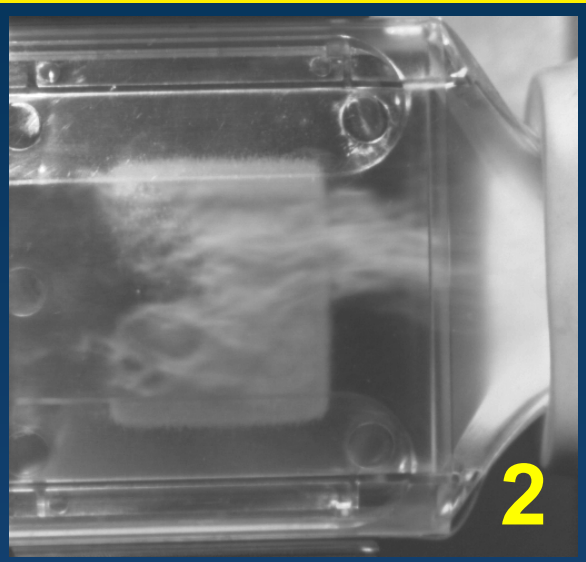

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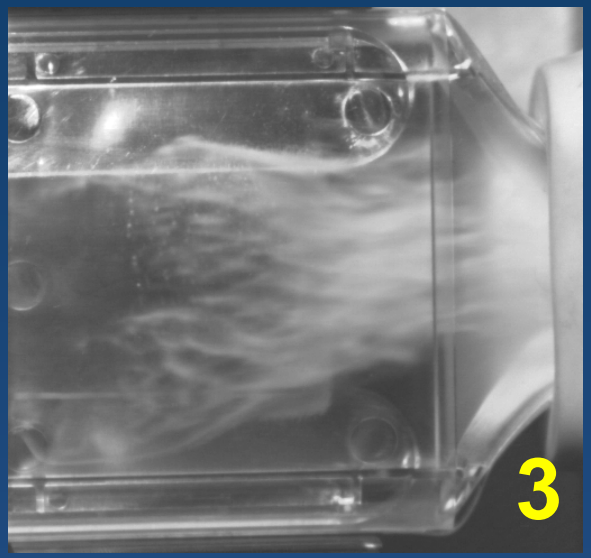
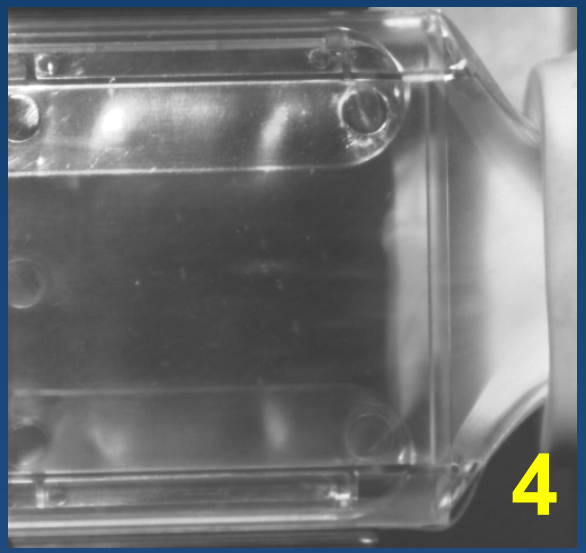
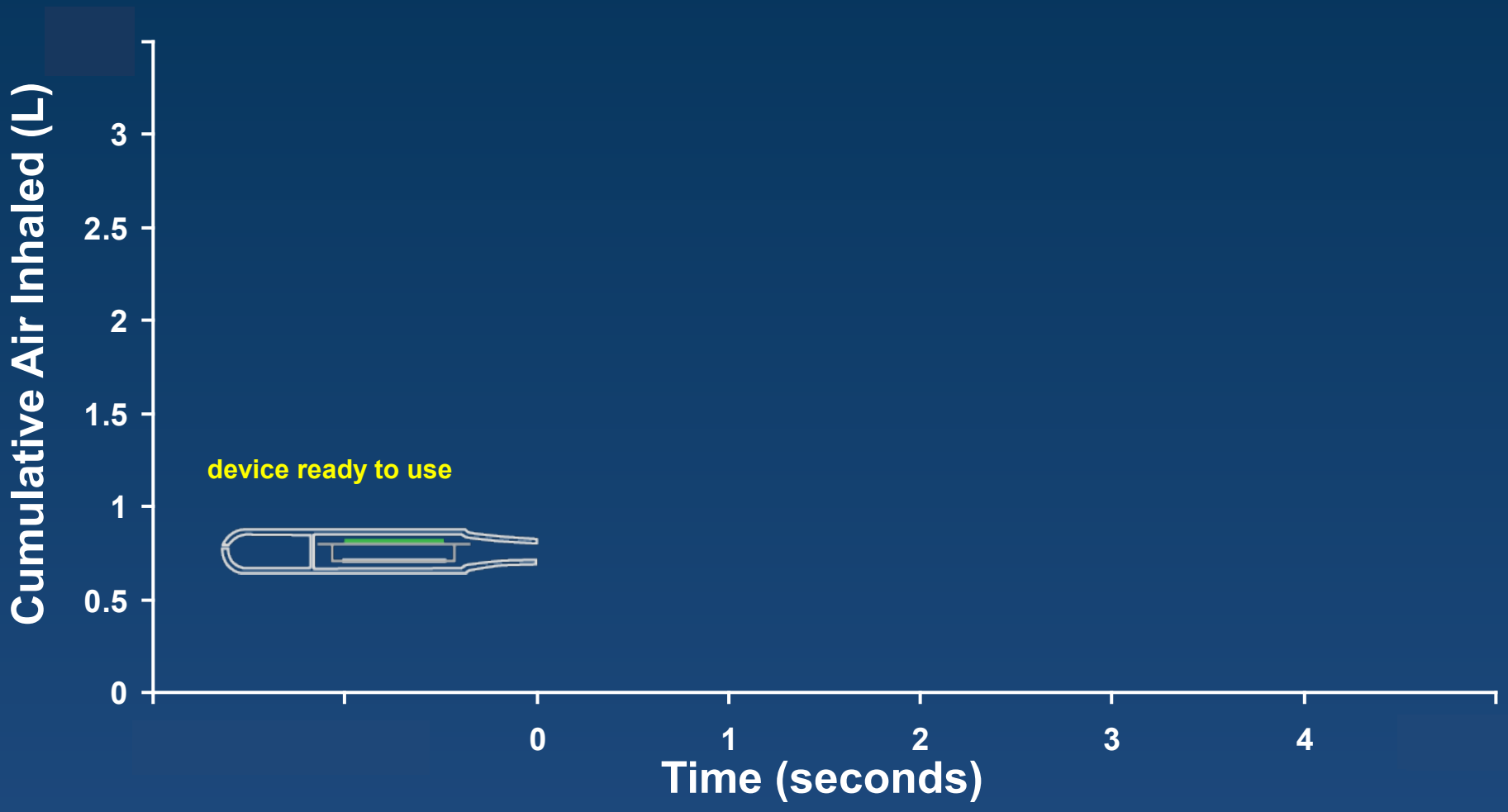




Time = 200 ms

Drug Delivered Early in a Single Breath



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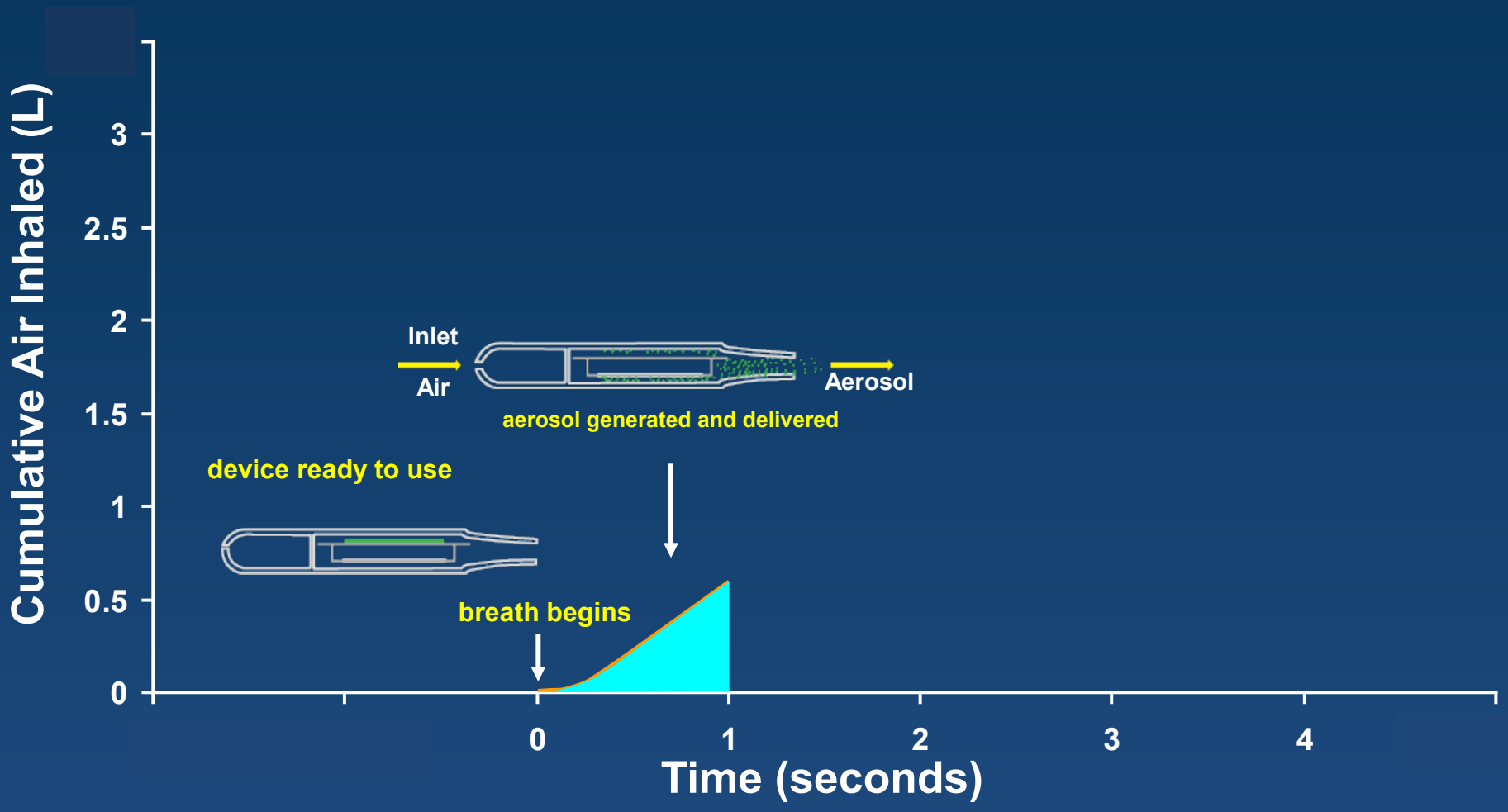

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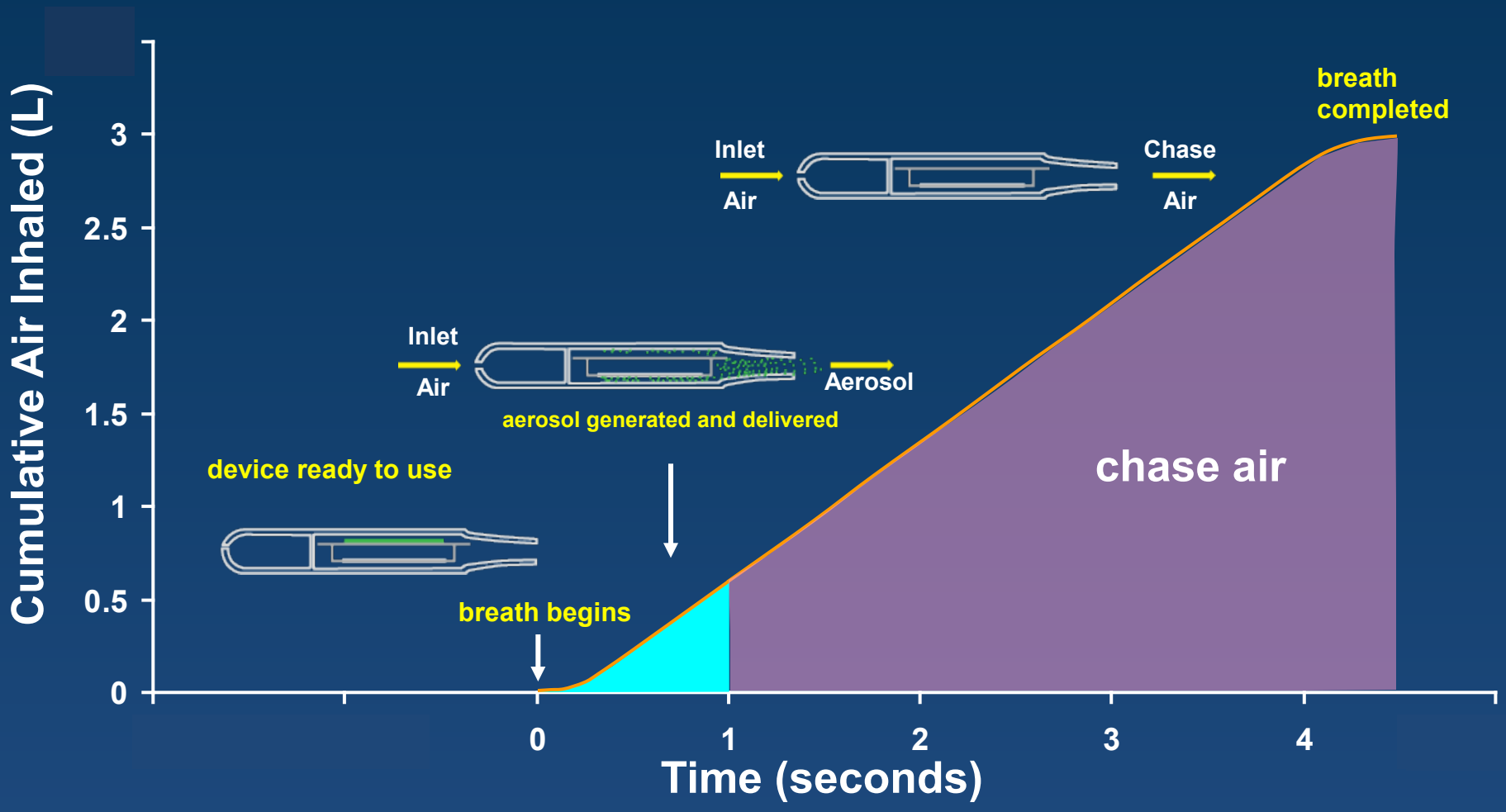
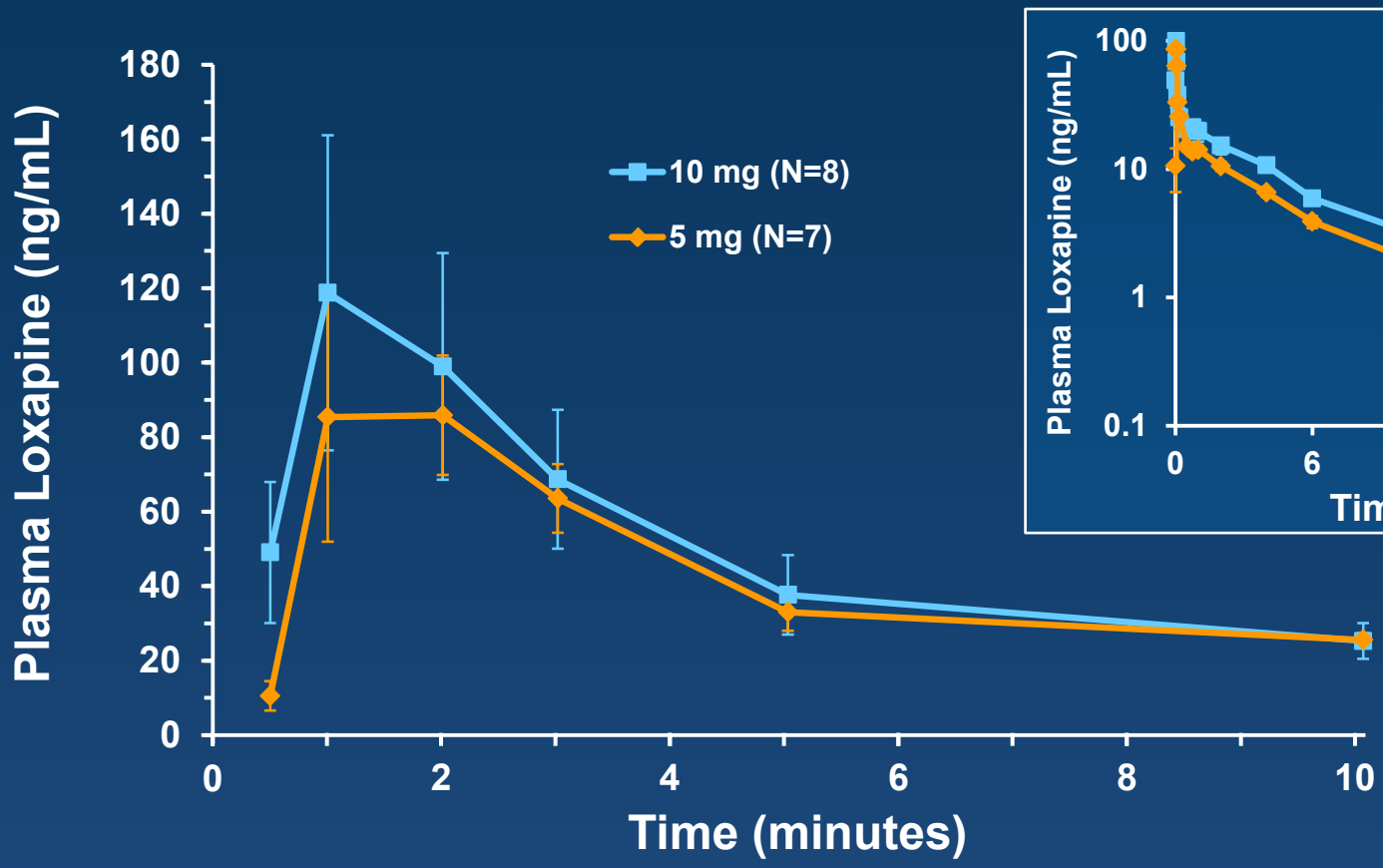
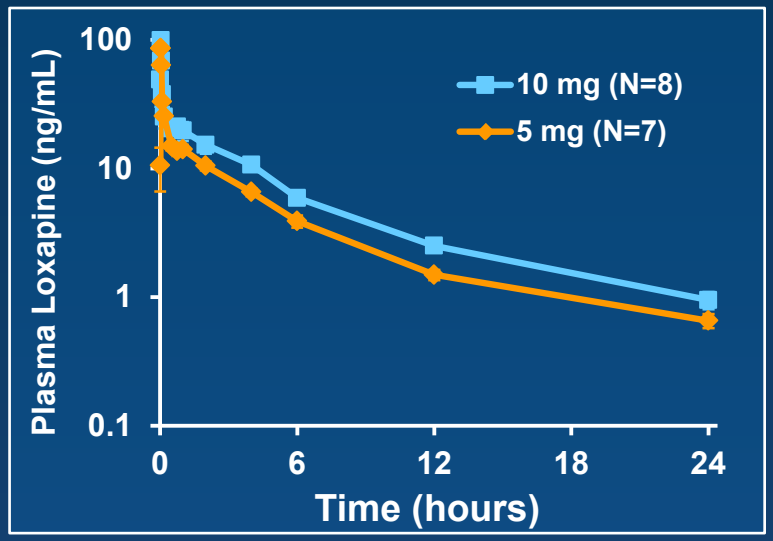


Loxapine: Medical and Technology Fit

- Loxapine delivered rapidly is well-suited for the acute treatment of agitation
- Loxapine is ideal for the Staccato system
  - Chemical purity ≥ 99.6%
    - High purity aerosol with negligible decomposition
  - Aerosol particle size approximately 2 µm
    - Optimal for lung deposition

ADASUVE PK Profile





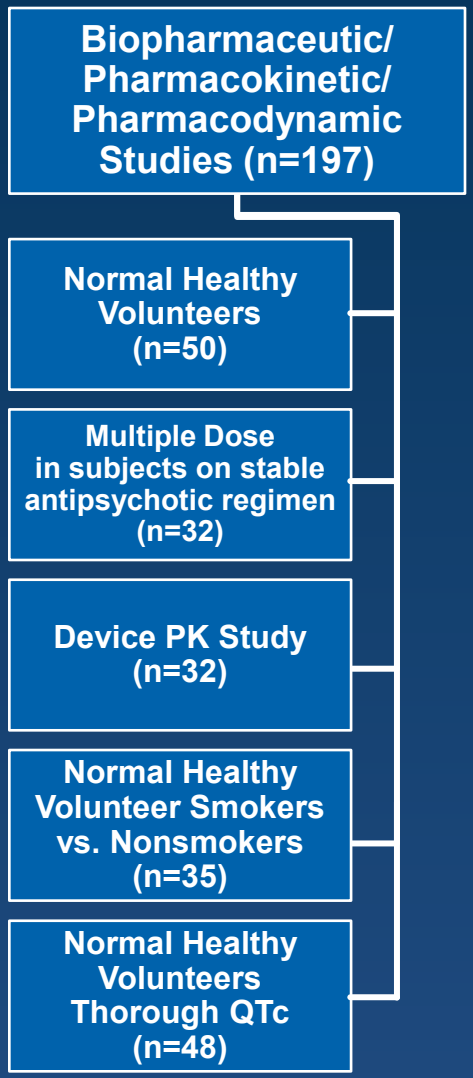
- **Across all Phase 1 doses:**
  - Median T_{max} = 2 min
  - Mean $T_{1/2}$ = 7.1 ± 1.5 hr

ADASUVE Efficacy

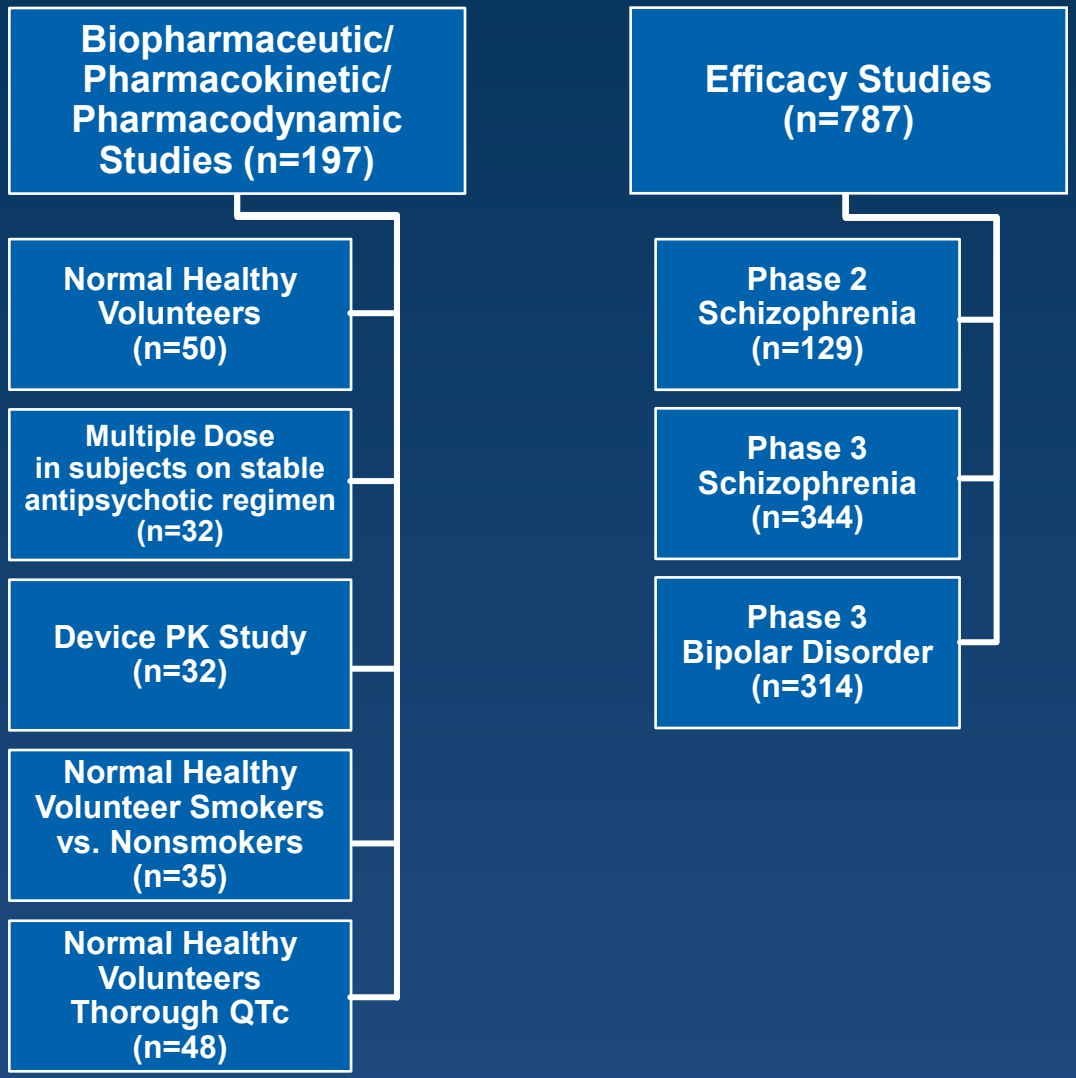
James Cassella, PhD

ADASUVE Clinical Program

ADASUVE Clinical Program



ADASUVE Clinical Program



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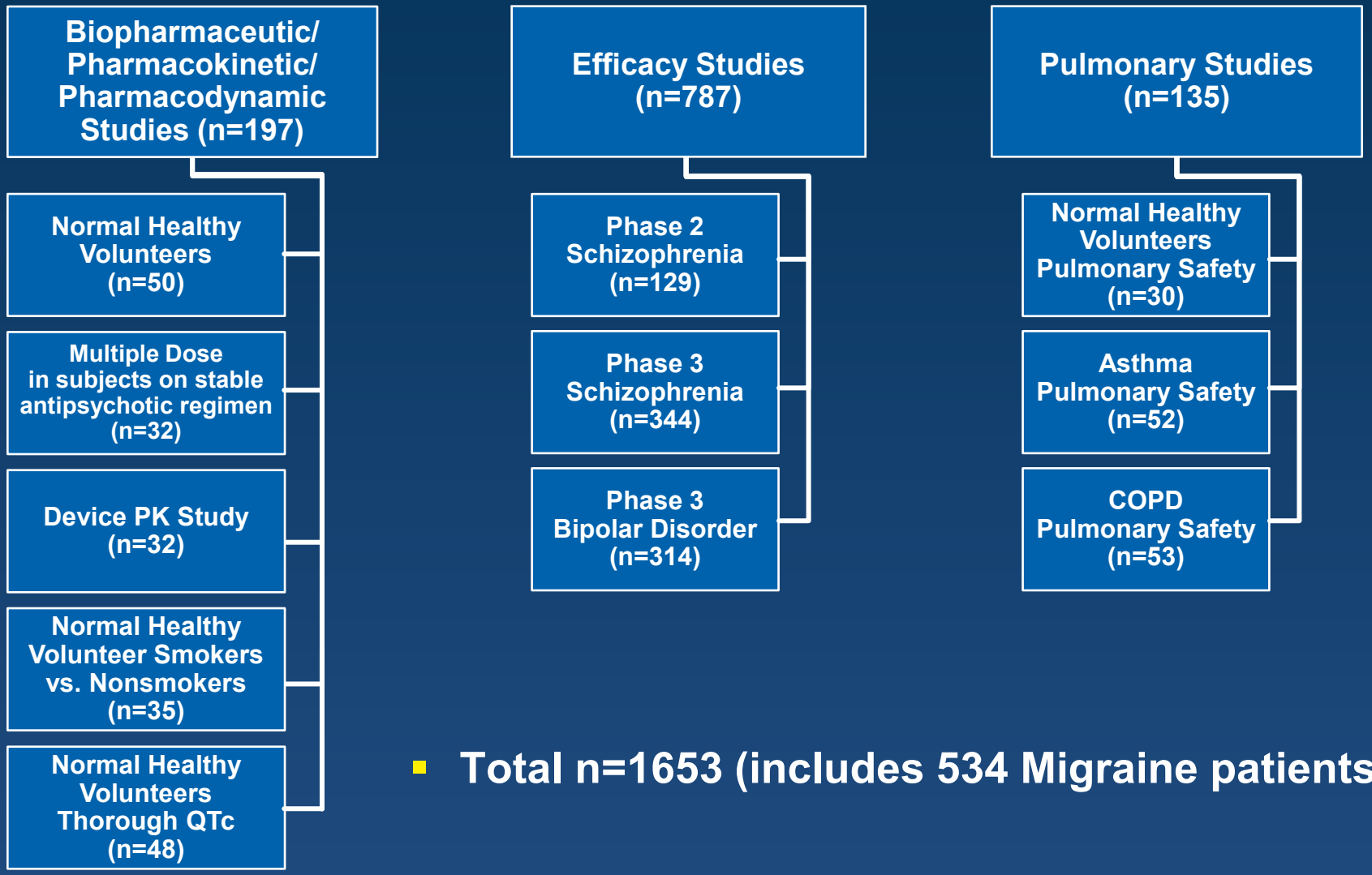
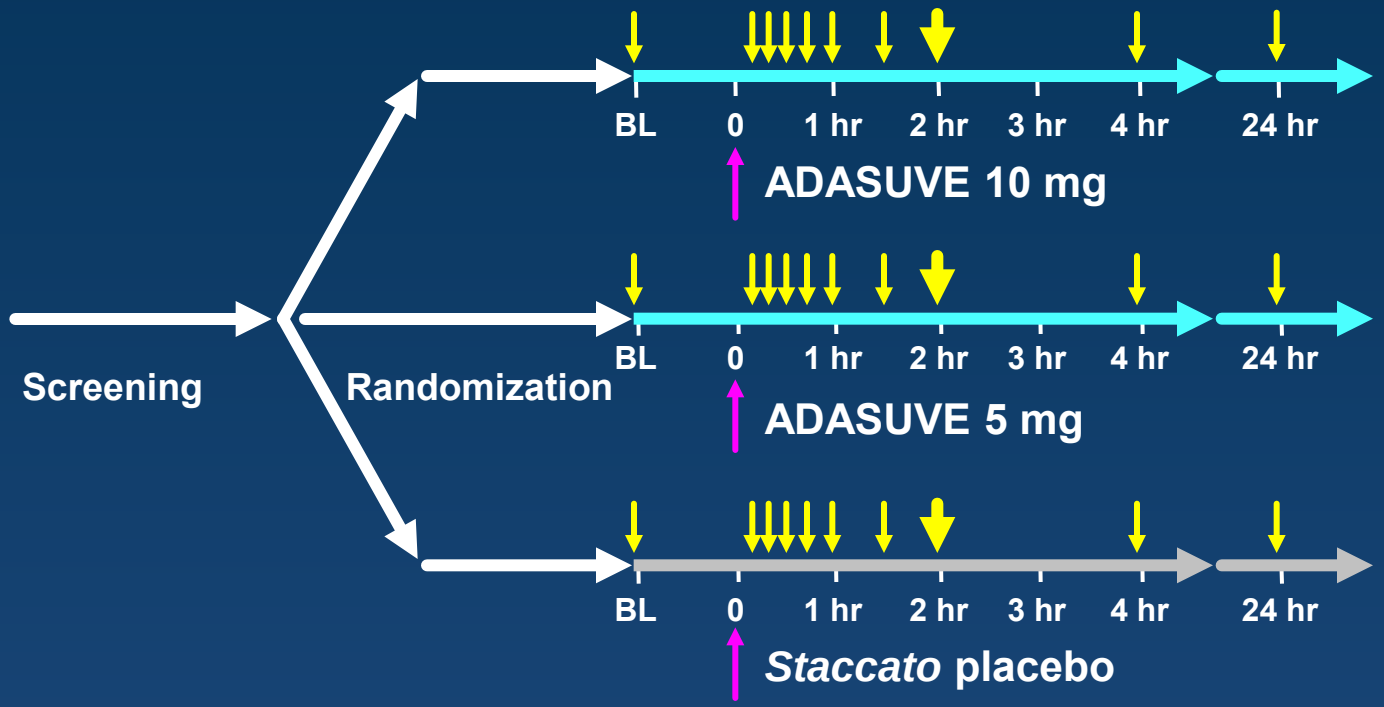


- Total n=1653 (includes 534 Migraine patients)

Design of Phase 3 Studies
Randomized, Double-blind, Placebo-controlled Trials



= Dosing

= PEC Assessment

= Primary Endpoint / Key Secondary Endpoint Assessment

- Dose 2 *prn* allowed > 2 hours after Dose 1
- Dose 3 *prn* allowed ≥ 4 hours after Dose 2
- Rescue drug (IM lorazepam) allowed after Dose 2

Device Training
ADASUVE Phase 3 Studies

- Screening
  - Patients asked to demonstrate an exhalation followed by slow, deep breath and breath hold (without any device)
  - No one failed this step
- Baseline (within 1 h of Study Drug administration)
  - Patient agitated – qualified for protocol; I/E criteria satisfied
  - Patients again asked to demonstrate an exhalation followed by slow, deep breath and breath hold
  - Plastic model with no working parts available
- Actual product used for dosing was not used at screening or baseline

ADASUVE Phase 3 Efficacy Endpoints
PANSS Excited Component (PEC) and CGI-Improvement

Primary Efficacy Endpoint:

- Change in PEC score from baseline to 2 h after Dose 1 of ADASUVE
- PEC items:
  - Poor impulse control
  - Tension
  - Hostility
  - Uncooperativeness
  - Excitement
- Each scored according to severity:
  - 1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = moderate-severe; 6 = severe; 7 = extreme
- Total score can range from 5 – 35

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Key Secondary Endpoint:

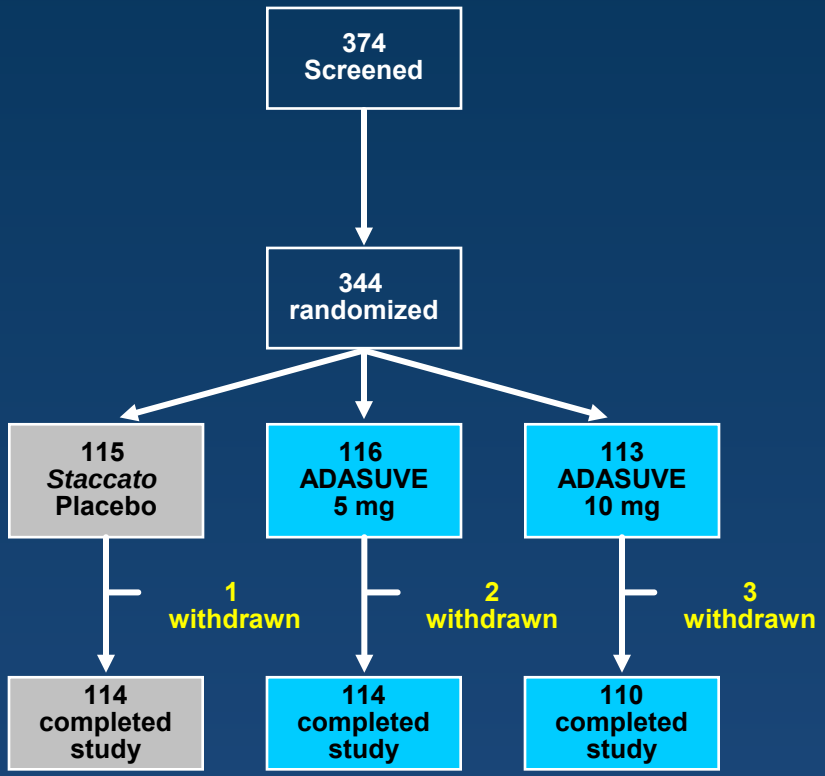
- Clinical Global Impression-Improvement (CGI-I) score at 2 h after Dose 1 of ADASUVE
  - 1 = very much improved
  - 2 = much improved
  - 3 = minimally improved
  - 4 = no change
  - 5 = minimally worse
  - 6 = much worse
  - 7 = very much worse

Additional Phase 3 Efficacy Endpoints and Analyses

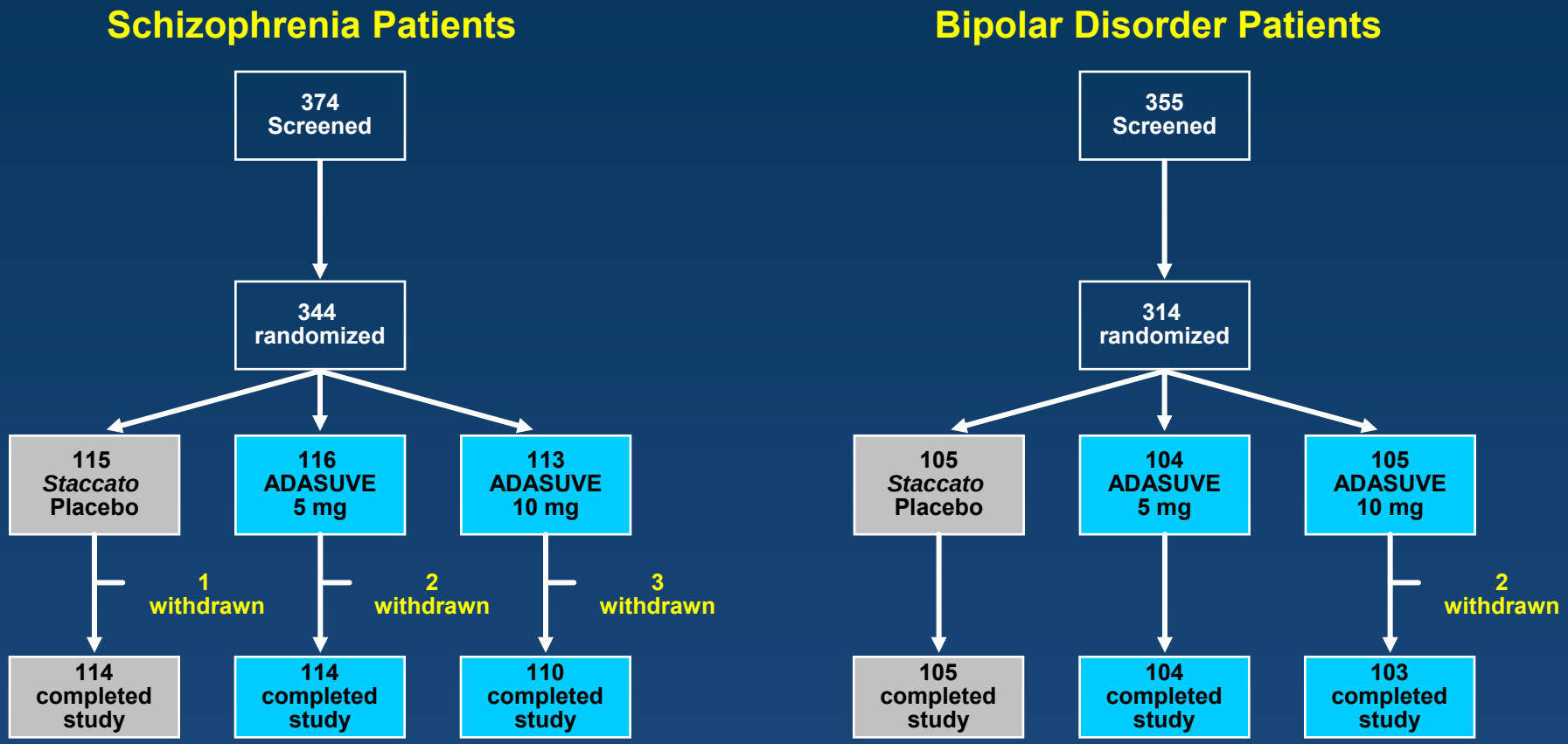
- **Key Predefined Analyses**
  - CGI-I Responder
  - Time to Dose 2
  - Changes from baseline in PEC score at 10, 20, 30, and 45 minutes (10 mg only)
- **Post Hoc Supportive Analyses**
  - Changes from baseline in PEC score for 5 mg (10 min – 24 h)
  - Individual PEC item scores
  - PEC 40 Responder

Phase 3 Study Disposition

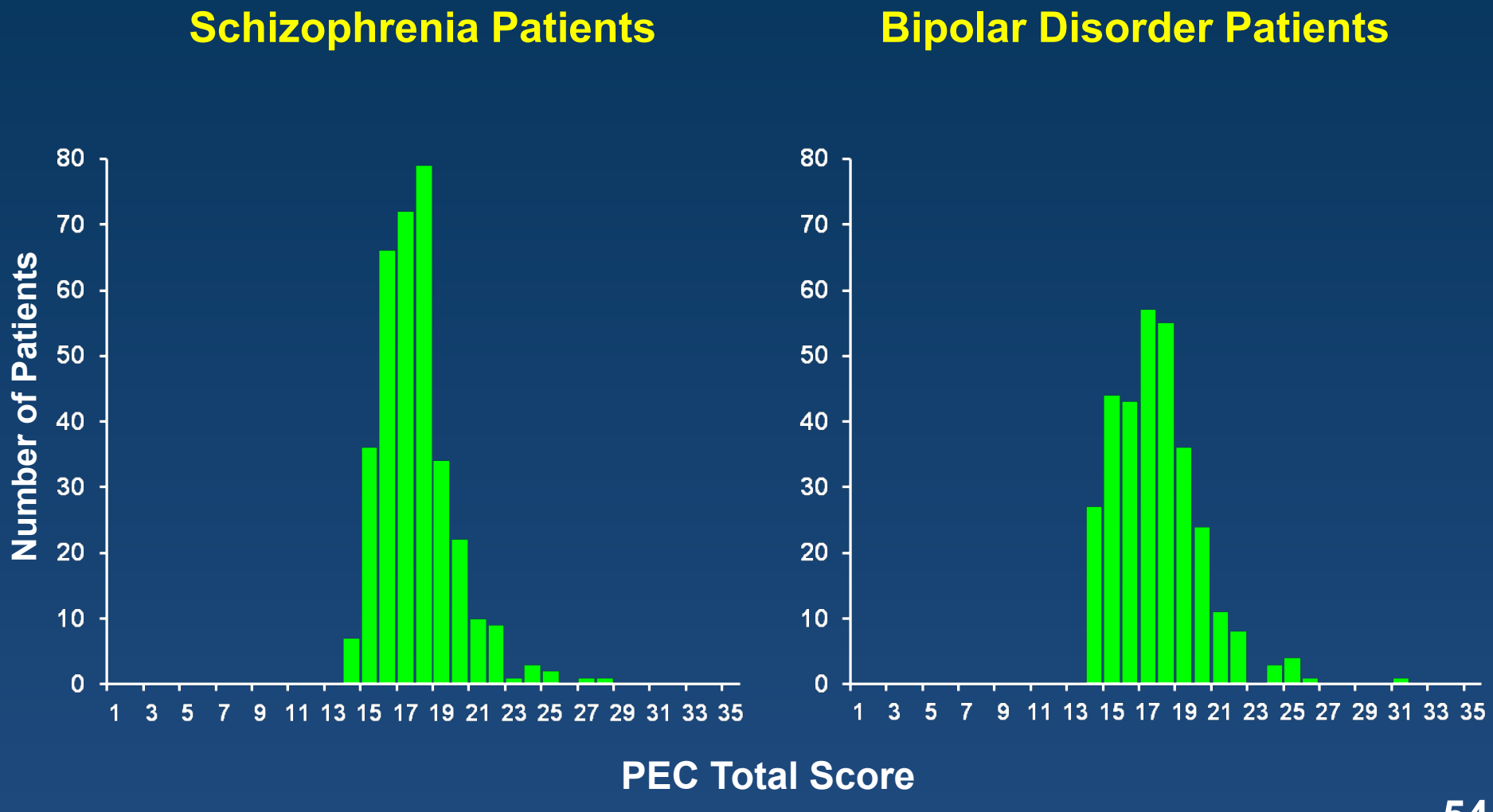
Schizophrenia Patients



Phase 3 Study Disposition



ADASUVE Phase 3
Baseline PEC Distribution



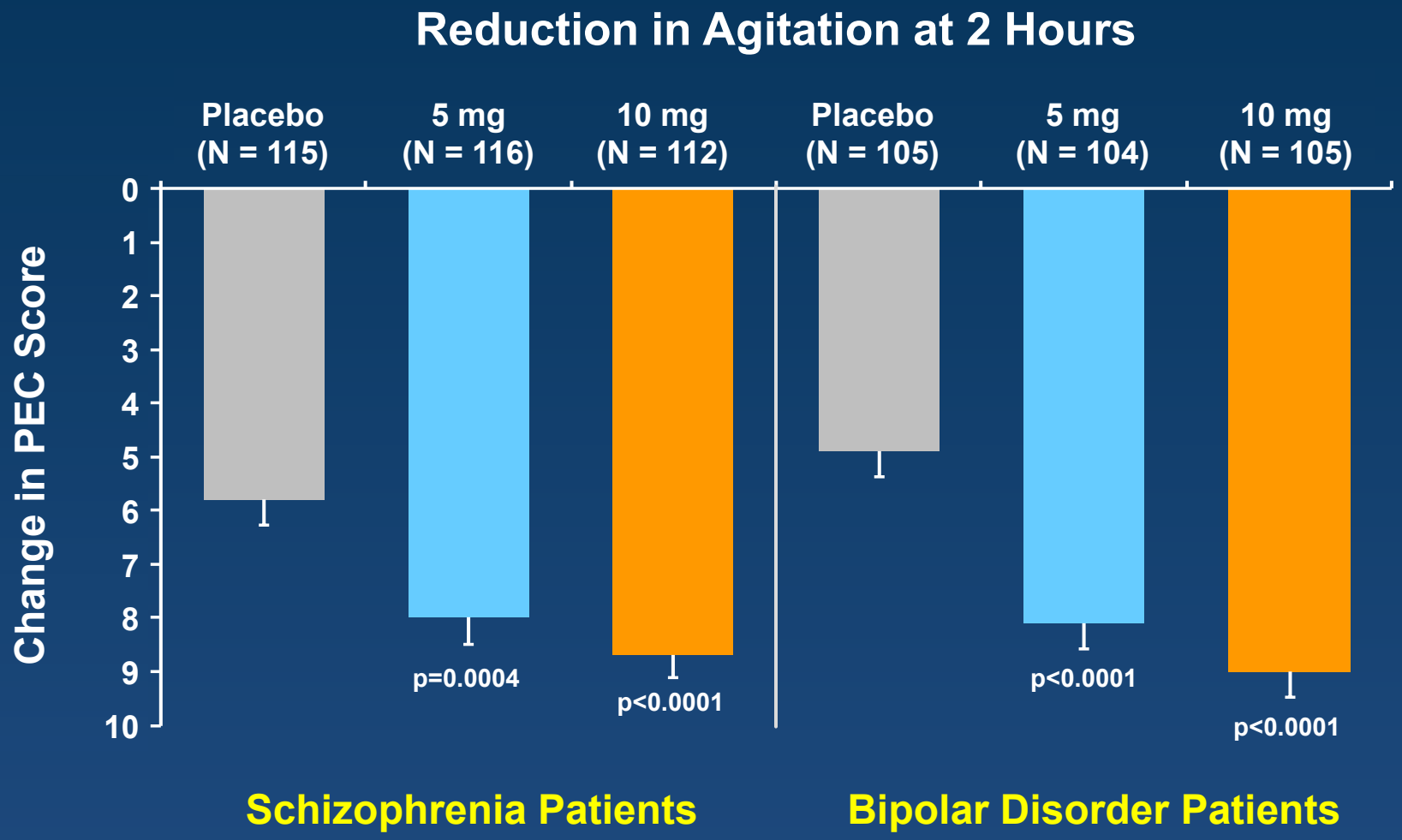
ADASUVE Phase 3 Patient Demographics

Demographics	Schizophrenia Patients			Bipolar Disorder Patients		
	Staccato Placebo (N=115)	ADASUVE 5 mg (N=116)	ADASUVE 10 mg (N=113)	*Staccato* Placebo (N=105)	ADASUVE 5 mg (N=104)	ADASUVE 10 mg (N=105)
Male, N (%)	80 (69.6)	87 (75.0)	86 (76.1)	56 (53.3)	47 (45.2)	53 (50.5)
Mean age (SD)	43.9 (9.45)	43.2 (10.24)	42.2 (9.82)	40.6 (9.82)	41.2 (9.63)	40.5 (9.80)
Race, N (%)						
Caucasian	32 (27.8)	48 (41.4)	36 (31.9)	33 (31.4)	58 (55.8)	47 (44.8)
Black	70 (60.9)	61 (52.6)	67 (59.3)	54 (51.4)	38 (36.5)	47 (44.8)
Other	13 (11.3)	7 (6.0)	10 (8.8)	18 (17.1)	8 (7.7)	11 (10.5)
Current smokers, N (%)	90 (78.3)	94 (81.0)	97 (85.8)	78 (74.3)	79 (76.0)	77 (73.3)

ADASUVE Phase 3 Psychiatric History

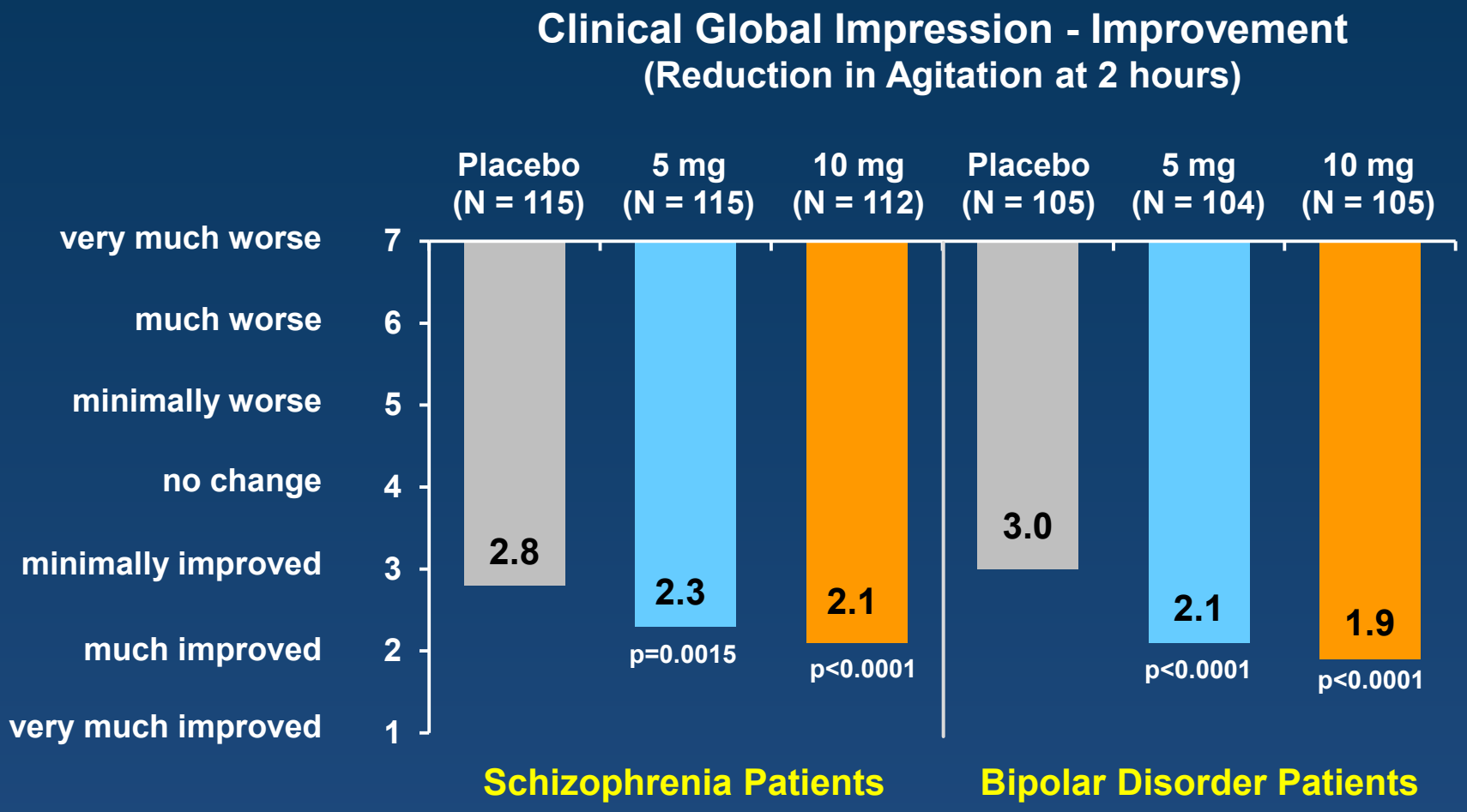
Baseline Characteristics	Schizophrenia Patients			Bipolar Disorder Patients		
	Staccato Placebo (N=115)	ADASUVE 5 mg (N=116)	ADASUVE 10 mg (N=113)	*Staccato* Placebo (N=105)	ADASUVE 5 mg (N=104)	ADASUVE 10 mg (N=105)
Time since diagnosis, Mean years (SD)	18.8 (10.34)	16.5 (10.80)	18.2 (10.03)	12.0 (10.09)	12.8 (8.91)	11.7 (9.05)
No. of previous hospitalizations, Mean (SD)	9.6 (8.96)	9.2 (12.22)	9.7 (11.26)	5.9 (6.57)	5.5 (6.55)	5.1 (6.41)
Baseline PEC score, Mean (SD)	17.4 (1.80)	17.8 (2.34)	17.6 (2.06)	17.7 (2.80)	17.4 (2.23)	17.3 (2.25)
Baseline CGI-S, Mean (SD)	3.9 (0.53)	4.0 (0.56)	4.1 (0.60)	4.1 (0.57)	4.0 (0.53)	4.0 (0.49)

Primary Endpoint

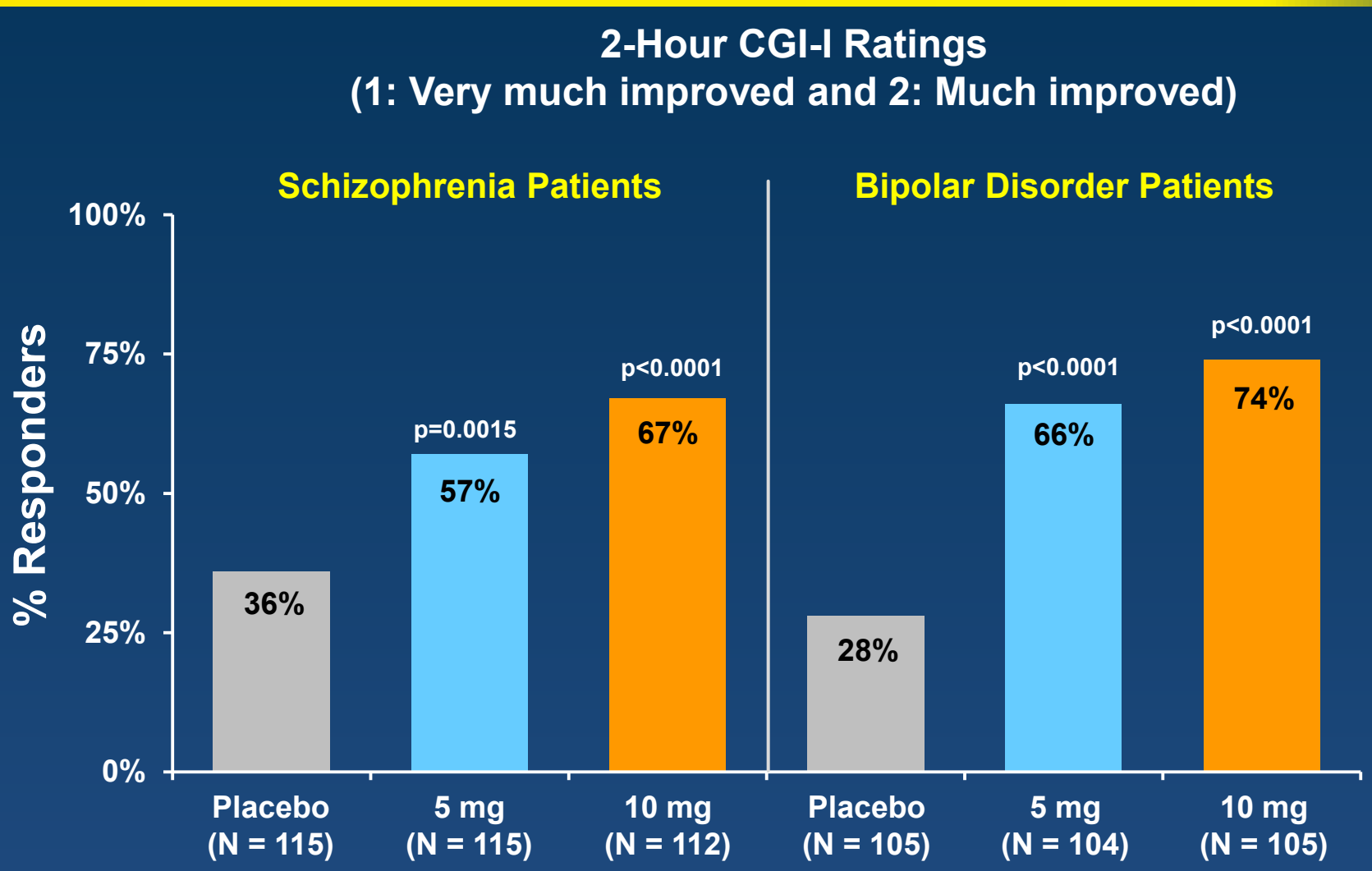


Mean ± SEM

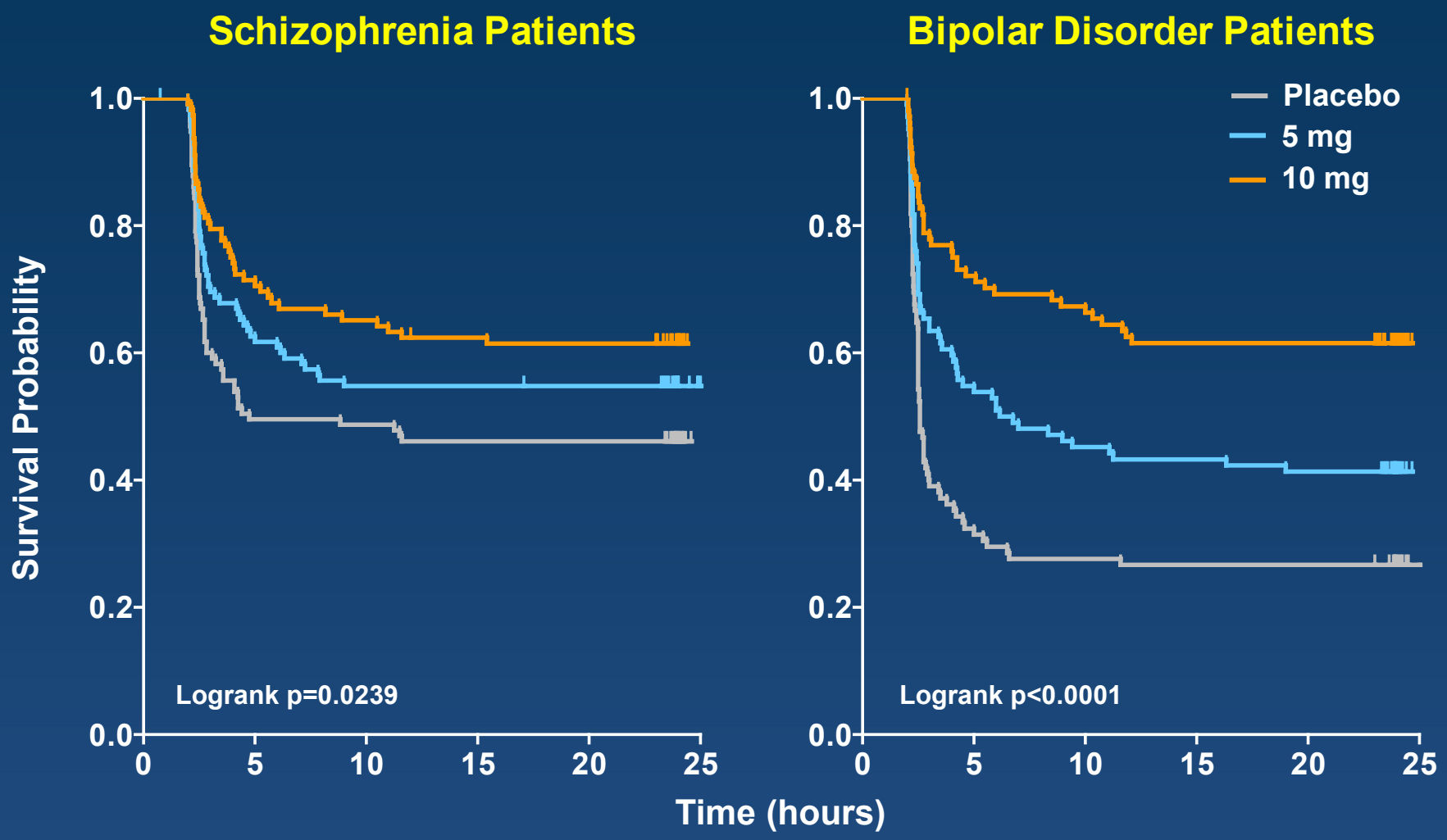
Key Secondary Endpoint



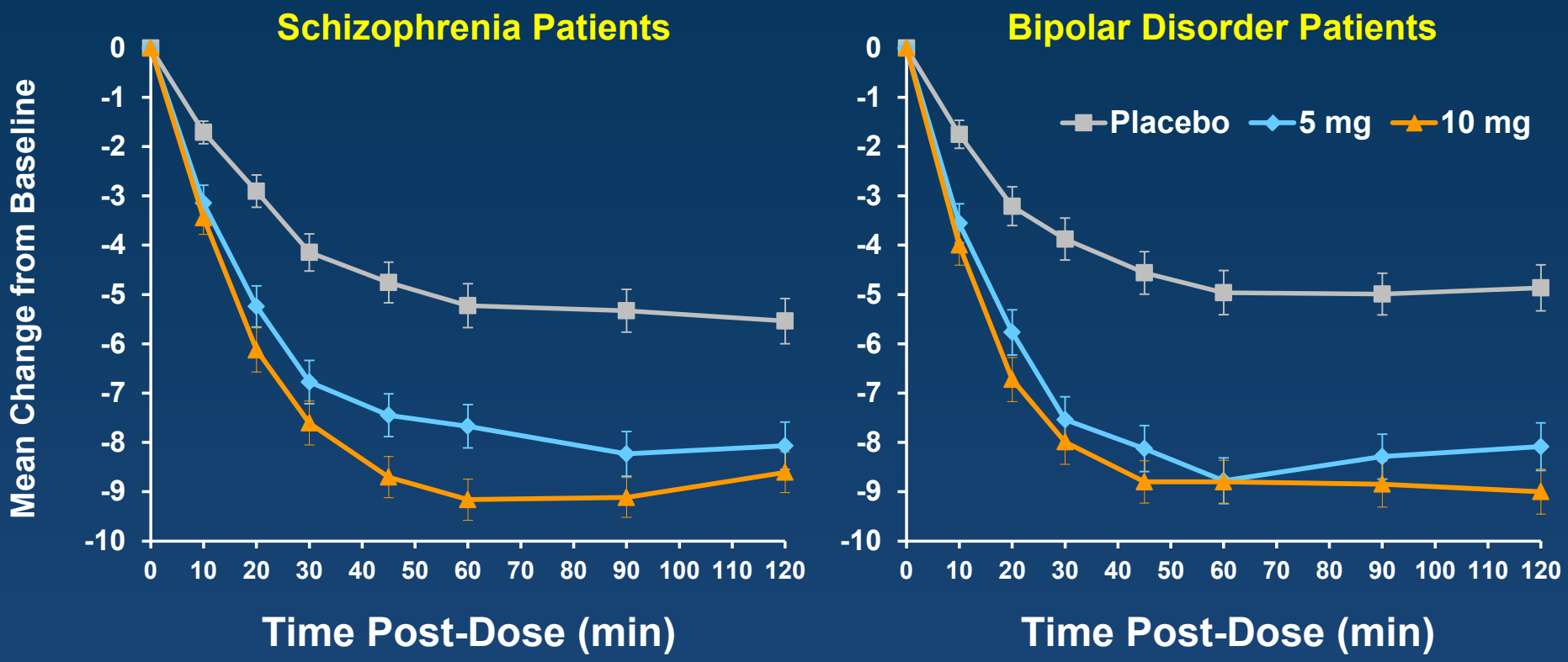
CGI-I Responder Analysis



Time to Dose 2

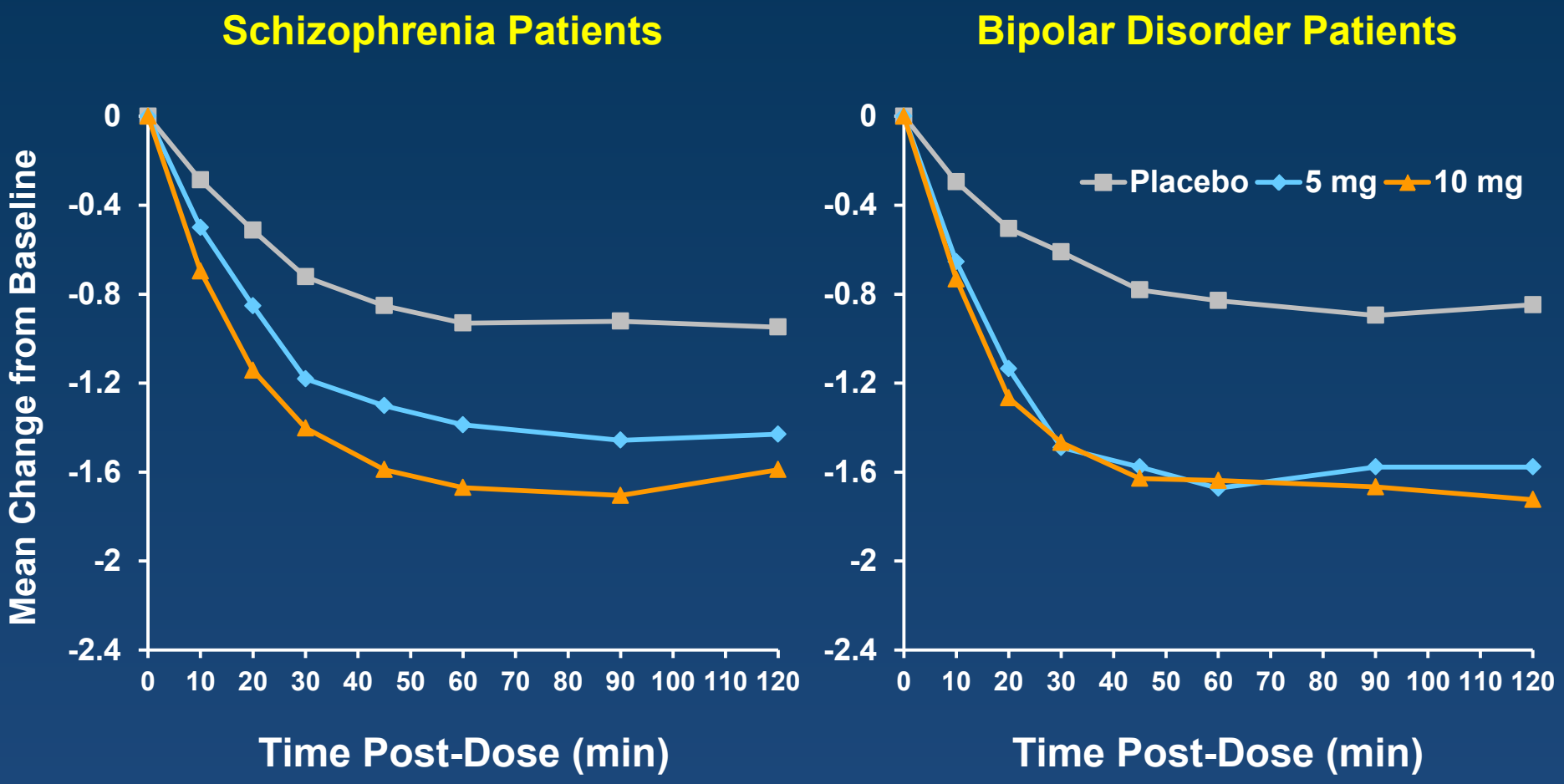


PEC Time Course



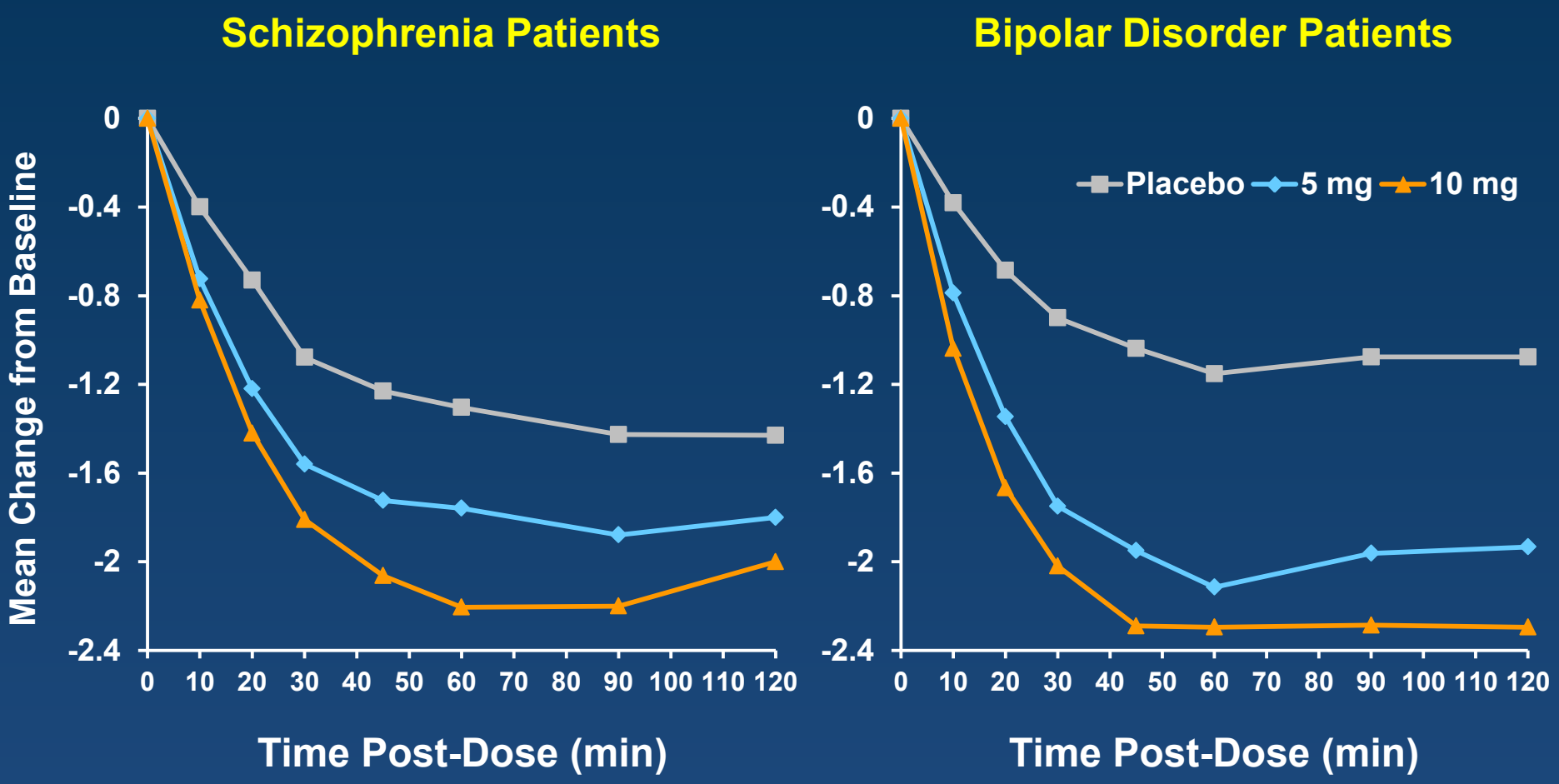
ADASUVE (10 mg)	10 min	20 min	30 min	45 min	60 min	90 min	2 hrs	4 hrs	24 hrs
Schizophrenia	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Bipolar Disorder	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.001

Change in Individual PEC Item: Poor Impulse Control



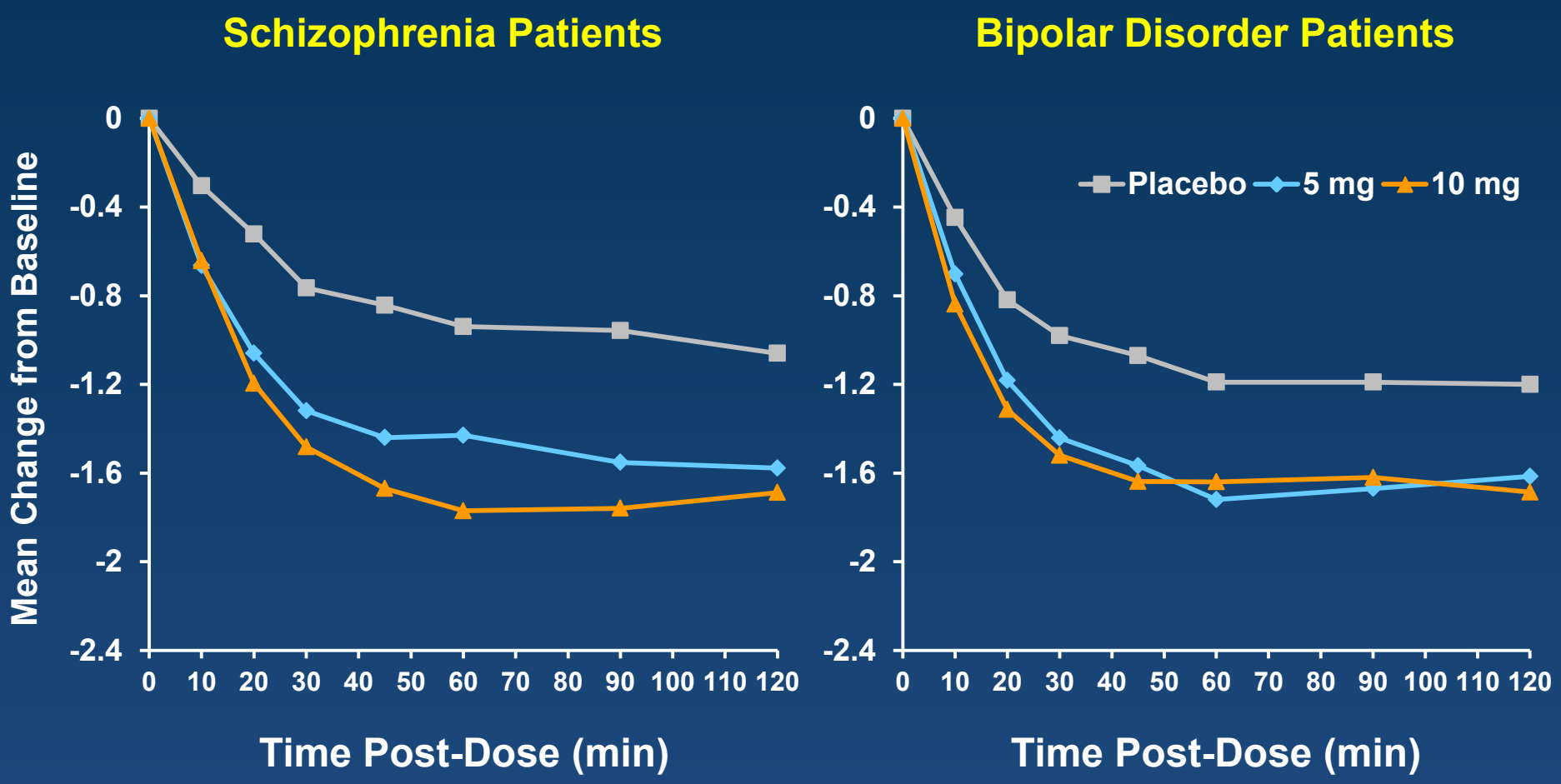
ADASUVE 5 mg and 10 mg statistically significant at all time points tested, except 5 mg 10 minute in schizophrenia only

Change in Individual PEC Item: Tension



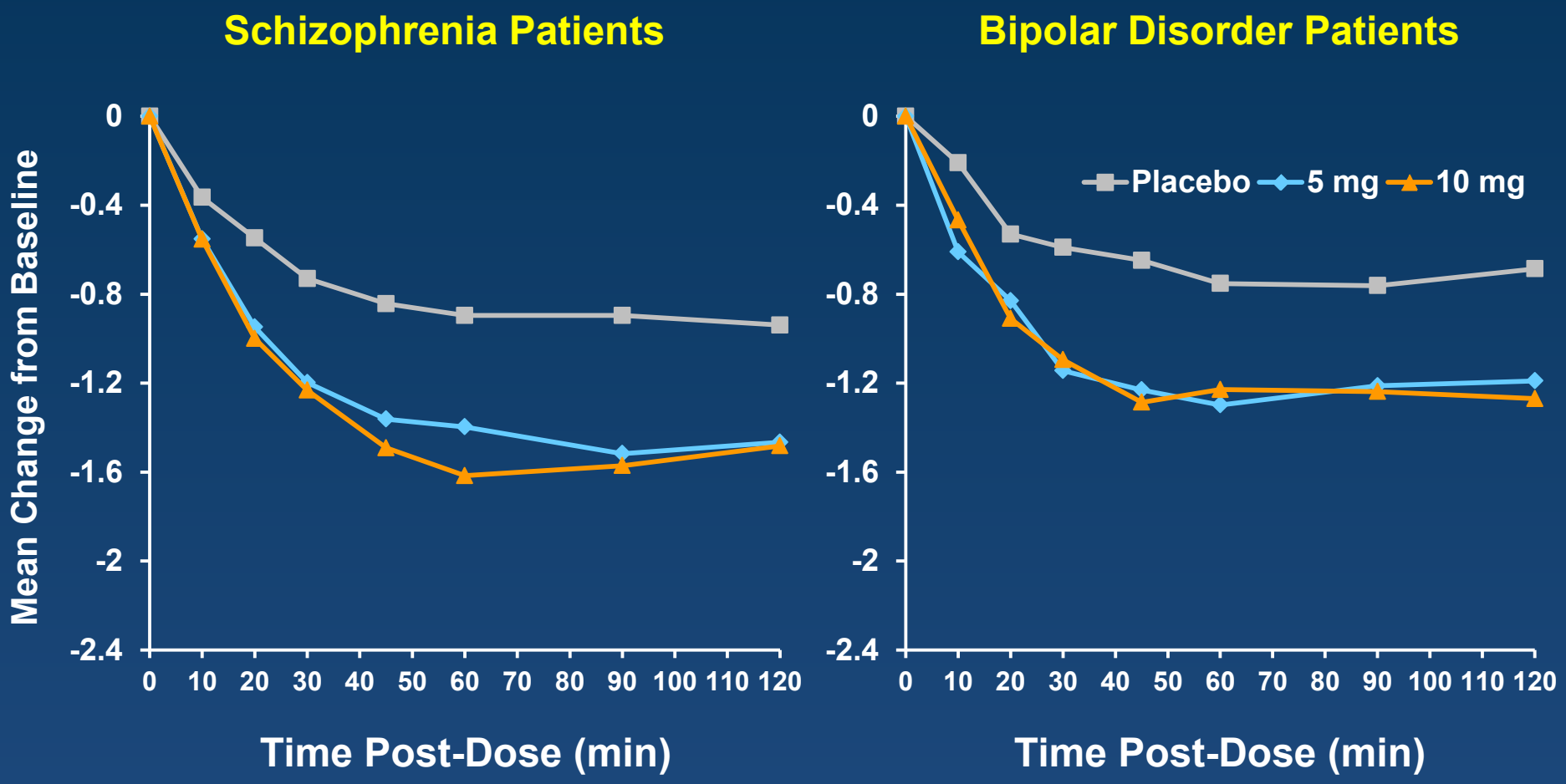
ADASUVE 5 mg and 10 mg statistically significant at all time points tested

Change in Individual PEC Item: Hostility



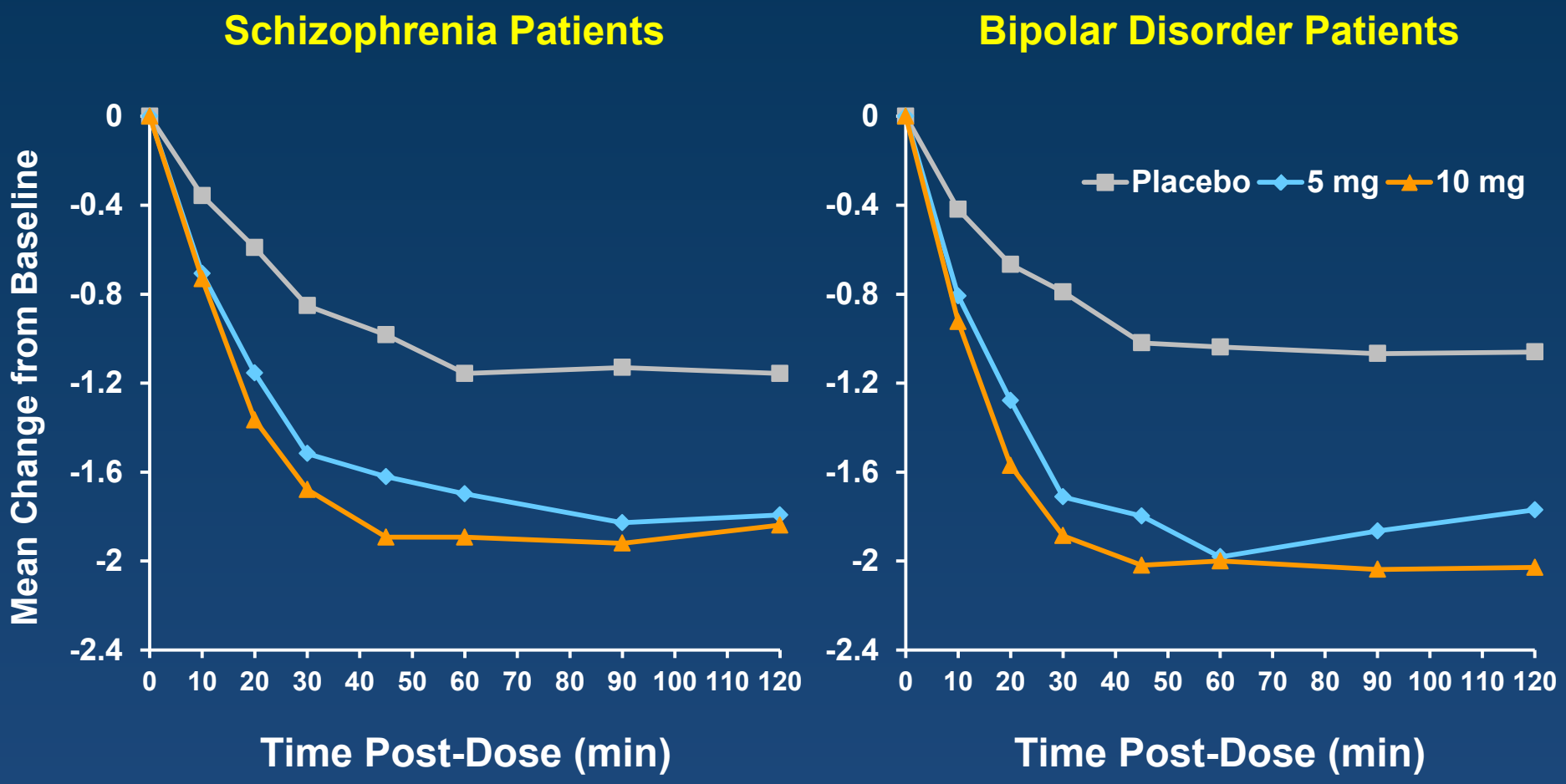
ADASUVE 5 mg and 10 mg statistically significant at all time points tested

Change in Individual PEC Item: Uncooperativeness



ADASUVE 5 mg and 10 mg statistically significant at all time points tested

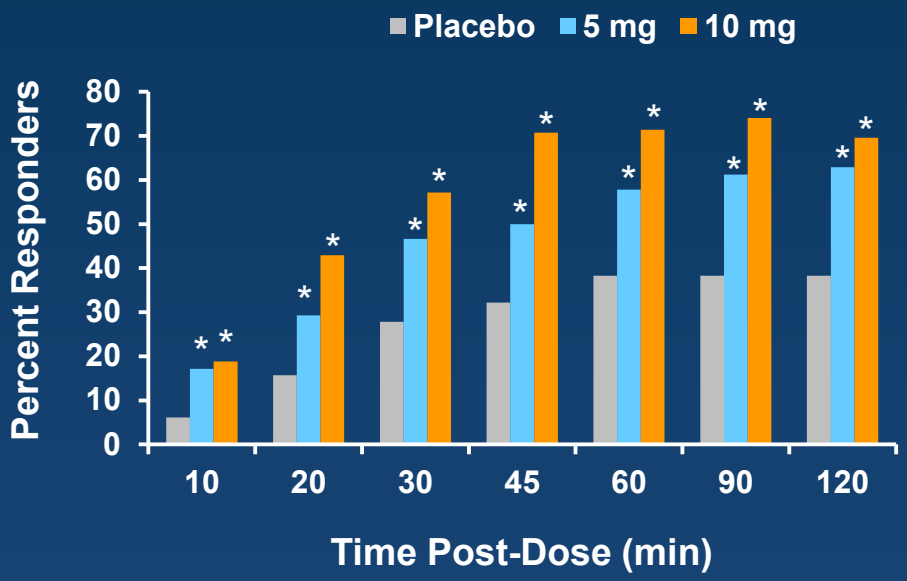
Change in Individual PEC Item: Excitement



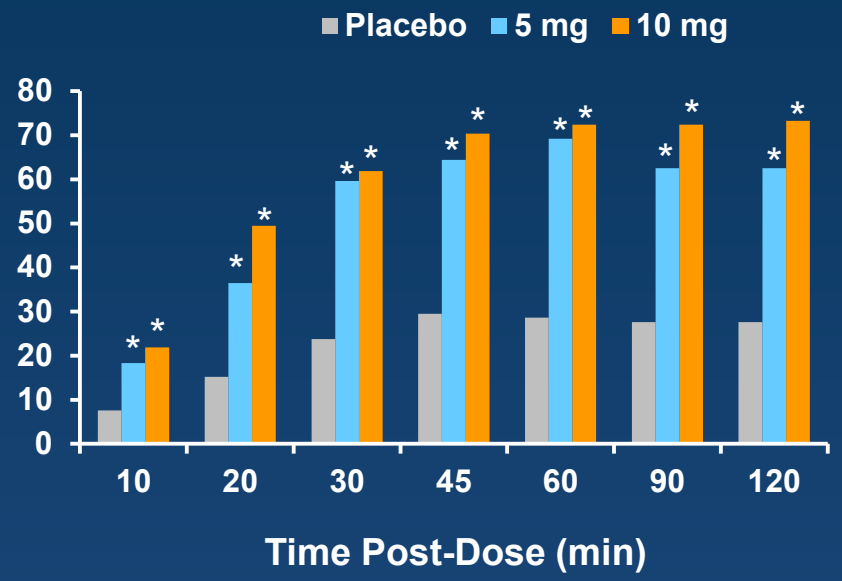
ADASUVE 5 mg and 10 mg statistically significant at all time points tested

PEC 40 Responder Analysis

Schizophrenia Patients



Bipolar Disorder Patients



Responder defined as achieving at least 40% reduction from baseline PEC

* p<0.01

Efficacy Conclusions

- The efficacy of ADASUVE was demonstrated in agitated patients from 2 distinct patient populations
  - These patients had long-standing schizophrenia or bipolar disorder
- Both the 5 and 10 mg doses met the primary and secondary endpoints
- Onset of treatment effect using the PEC scale was evident at 10 minutes post-dosing in both patient groups
  - Support for the rapid onset was derived from the PEC responder analysis and individual PEC item analysis
- Across multiple endpoints, the magnitude of the treatment effect was larger in the 10 mg group than the 5 mg group

Clinical Safety Review

Robert Fishman, MD, FCCP
VP, Clinical Development
Alexza Pharmaceuticals

Clinical Safety Review

- Extent of exposure
- General safety of ADASUVE
  - Adverse reactions
  - Serious adverse events and discontinuations
- Safety topics of interest
  - CNS effects
  - Pulmonary safety

Number of Study Patients / Subjects Treated with ADASUVE or Placebo

Analysis Population / Patient Type (N)		Placebo (N=578)	ADASUVE Dose <5 mg (N=348)	ADASUVE Dose 5 mg (N=347)	ADASUVE Dose 10 mg (N=452)	All ADASUVE (N=1147)
Agitated Patients Population	Ph 2 Schiz	43	NA	45	41	86
	Ph 3 Schiz	115	NA	116	113	229
	Ph 3 BD	105	NA	104	105	209
		263	NA	265	259	524

Number of Study Patients / Subjects Treated with ADASUVE or Placebo

Analysis Population / Patient Type (N)		Placebo (N=578)	ADASUVE Dose <5 mg (N=348)	ADASUVE Dose 5 mg (N=347)	ADASUVE Dose 10 mg (N=452)	All ADASUVE (N=1147)
Agitated Patients Population	Ph 2 Schiz	43	NA	45	41	86
	Ph 3 Schiz	115	NA	116	113	229
	Ph 3 BD	105	NA	104	105	209
		263	NA	265	259	524
Healthy volunteer population		90	21	23	133	177
Subjects on stable antipsychotic regimens		8	NA	16	8	24
Subjects with asthma		26	NA	NA	26	26
Subjects with COPD		27	NA	NA	26	26
Patients with migraine headache		164	327	43	NA	370
TOTAL		578	348	347	452	1147

Adverse Reactions
Phase 2/3 Agitated Patients

AEs with an ADASUVE Incidence ≥ 2% and > Placebo

MedDRA System Organ Class Preferred Term, N (%)	Placebo (N=263)	ADASUVE Dose 5 mg (N=265)	ADASUVE Dose 10 mg (N=259)
Dysgeusia	13 (4.9%)	30 (11.3%)	37 (14.3%)
Sedation/Somnolence	25 (9.5%)	32 (12.1%)	31 (12.0%)
Fatigue	5 (1.9%)	6 (2.3%)	3 (1.2%)
Throat Irritation	1 (0.4%)	2 (0.8%)	7 (2.7%)

Serious Adverse Events and Discontinuations

	Serious Adverse Events (N)	Discontinuations for AEs (N)
Placebo (N=578)	Schizophrenia: 1 Appendicitis: 1 Apparent overdose of illicit IV drug: 1	Appendicitis: 1
ADASUVE < 5 mg (N=348)	None	None
ADASUVE 5 mg (N=347)	Hypertension: 1	Urticaria: 1
ADASUVE 10 mg (N=452)	Schizophrenia: 1 Gastroenteritis: 1	Upper respiratory tract infection: 1 Bronchospasm: 1 Anxiety: 2

CNS Adverse Events
Phase 2/3 Agitated Patients

Nervous System AEs Experienced by 2 or More Patients

MedDRA System Organ Class Preferred Term, N (%)	Placebo (N=263)	ADASUVE Dose 5 mg (N=265)	 10 mg (N=259)
Pts. with any nervous system AE	**58 (22.1%)**	**55 (20.8%)**	**51 (19.7%)**
Sedation/Somnolence	25 (9.5%)	32 (12.1%)	31 (12.0%)
Dizziness	23 (8.7%)	17 (6.4%)	19 (7.3%)
Headache	26 (9.9%)	9 (3.4%)	8 (3.1%)
Akathisia	0	1 (0.4%)	1 (0.4%)
Tremor	0	2 (0.8%)	0

Pulmonary Safety in ADASUVE Treated Subjects

Subjects without active airways disease (N=1095)	Subjects with active airways disease (N=52)

Pulmonary Safety in ADASUVE Treated Subjects

Subjects without active airways disease (N=1095)

Subjects with active airways disease (N=52)

Agitated patient population
Included smokers

Healthy volunteers and other subjects in overall safety population

Pulmonary Safety: Airway Adverse Events Phase 2/3 Agitated Patients

Airway Adverse Event Preferred Term, N (%)	Placebo (N=263)	ADASUVE Dose 5 mg (N=265)	ADASUVE Dose 10 mg (N=259)
Wheezing	0	2 (0.8%)	0
Bronchospasm	0	0	1 (0.4%)
Cough	0	0	1 (0.4%)

- 87% of agitated patients were smokers
- 7% of agitated patients had a history of asthma or COPD
  - None of these patients had an airway AE

Pulmonary Safety: Airway Adverse Events Phase 2/3 Agitated Patients

Airway Adverse Event Preferred Term, N (%)	Placebo (N=263)	ADASUVE Dose 5 mg (N=265)	ADASUVE Dose 10 mg (N=259)
Wheezing	0	2 (0.8%)	0
Bronchospasm	0	0	1 (0.4%)
Cough	0	0	1 (0.4%)

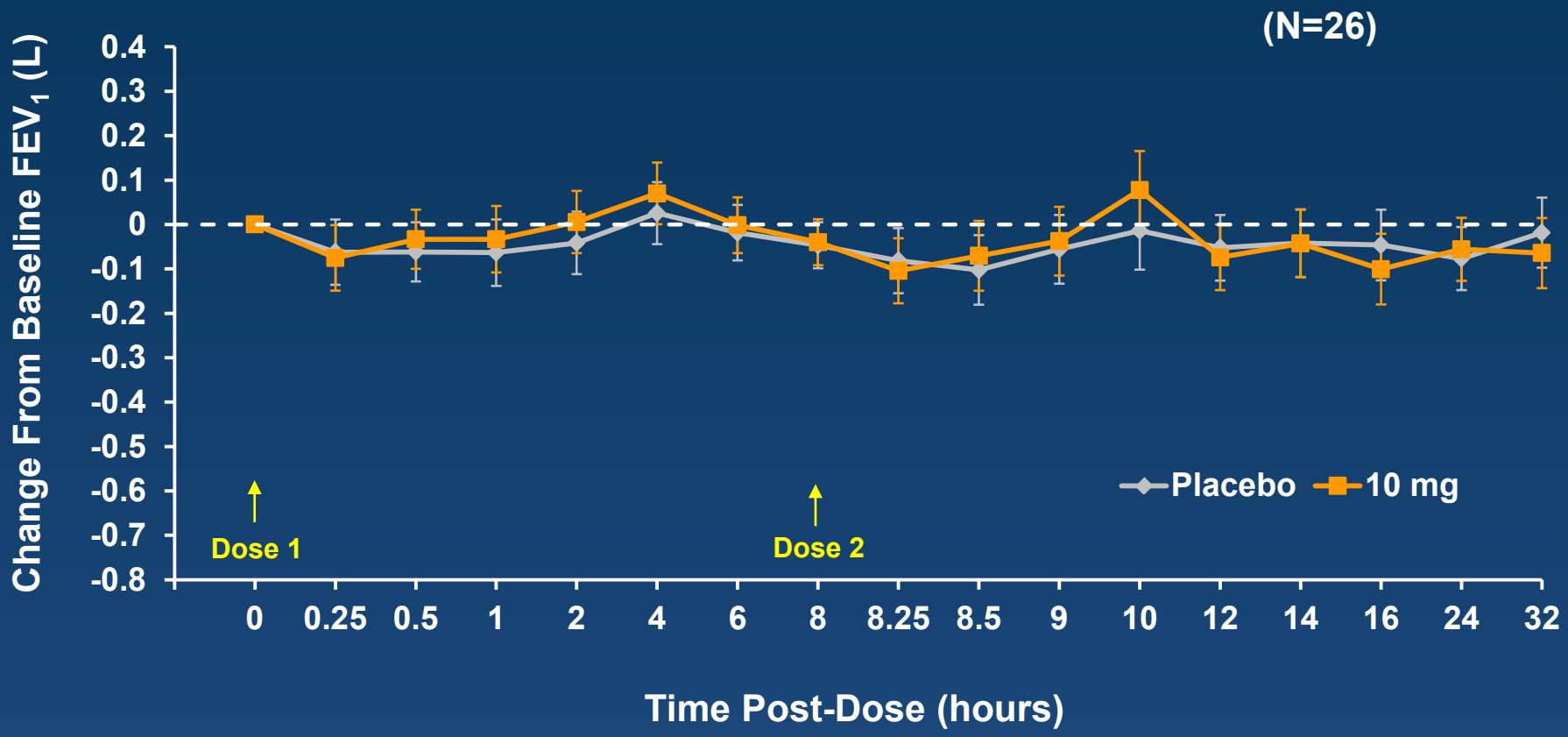
- 87% of agitated patients were smokers
- 7% of agitated patients had a history of asthma or COPD
  - None of these patients had an airway AE

- Among all ADASUVE-treated subjects without active airways disease, 1/1095 (0.09%) required treatment with a bronchodilator

Pulmonary Safety Study in Nonsmoking Healthy Volunteers

- Randomized, double-blind, 2-treatment, 2-way crossover
- Nonsmokers, 18-65 years old
  - Treatments at 0 and 8 hours
  - *Staccato* Placebo x 2
  - ADASUVE 10 mg x 2
- Primary outcome measure:
  - Change in FEV_1 from baseline (16 post-treatment tests)

Change in FEV_1 from Same-Period Baseline in Healthy Volunteers



LSmeans and 90% LSmean CI

Results of Pulmonary Safety Study in Healthy Volunteers

- No respiratory AEs
- Transient decreases in FEV_1 ≥10% were seen in both treatment groups
  - In completers: ADASUVE, 7 subjects
    Placebo, 7 subjects

Results of Pulmonary Safety Study in Healthy Volunteers

- No respiratory AEs
- Transient decreases in FEV_1 ≥10% were seen in both treatment groups
  - In completers: ADASUVE, 7 subjects
    Placebo, 7 subjects
- In all cases, no indication of bronchospasm
  - No evidence of treatment-induced obstruction
  - Flow-volume loops show multiple instances of suboptimal and/or variable test efforts
  - No significant changes in respiratory rate, O_2 saturation or heart rate

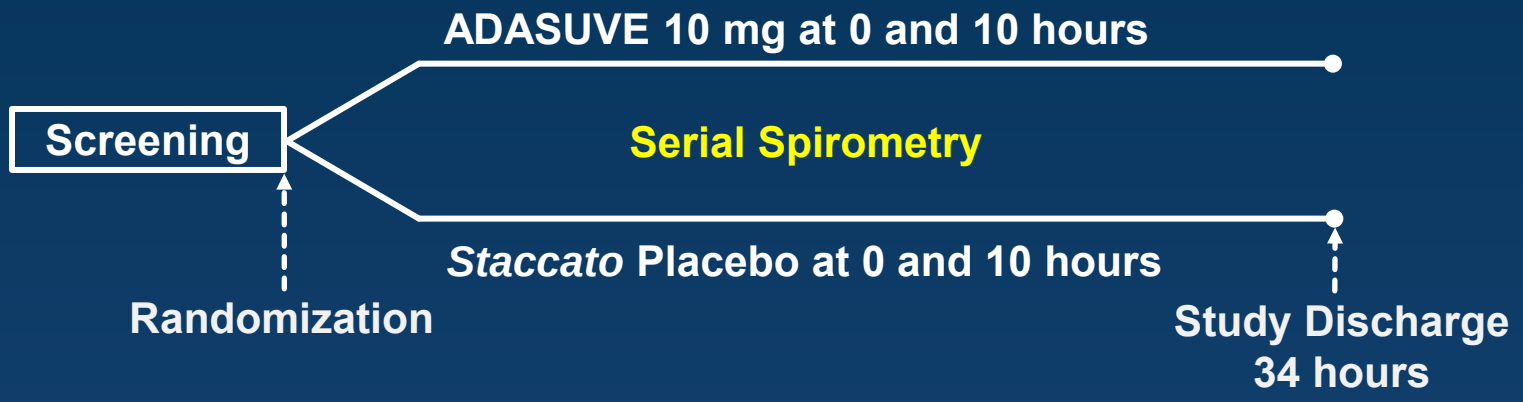
Pulmonary Safety in ADASUVE Treated Subjects

Subjects without active airways disease (N=1095)

Subjects with active airways disease (N=52)

- **Asthma**
- **COPD**

Pulmonary Safety Studies in Subjects with Asthma or COPD

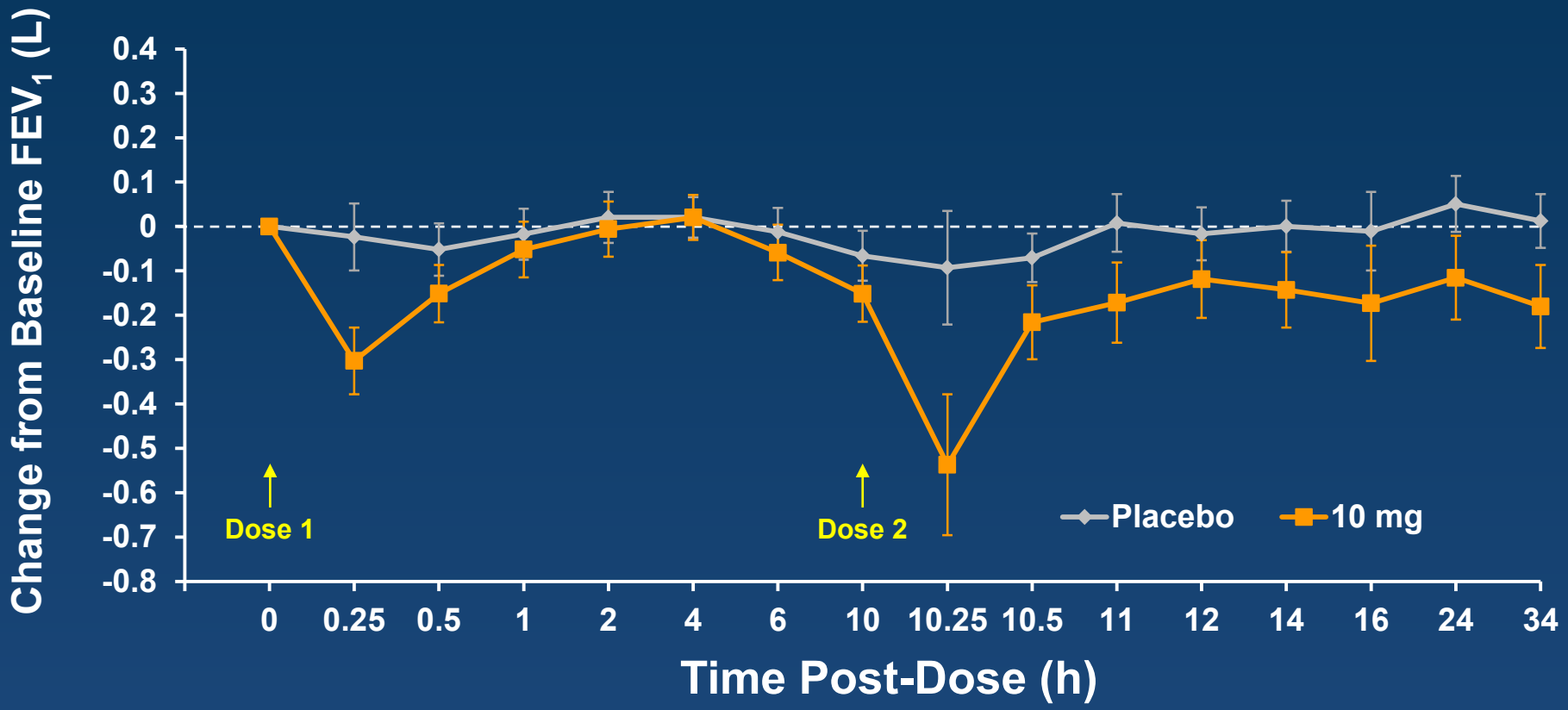


- Populations
  - Mild to moderate persistent asthma (N=52)
  - COPD with $FEV_1 \geq 40\%$ predicted (N=53)
- Quick-relief agents withheld
- Controller agents continued
- Primary outcome measure:
  - Change in FEV_1 from baseline (15 post-treatment tests)

Asthma Severity at Screening Asthma Study

	N = 52
Asthma classification at screening (NHLBI guideline), N (%):	
FEV_1 in Well Controlled category (FEV_1 >80% of predicted)	34 (65.4%)
FEV_1 in Not Well Controlled category (FEV_1 60-80% of predicted)	18 (34.6%)
Screening pre-bronchodilator FEV_1 (% of predicted), median (range)	85.5% (60.0% - 117.0%)

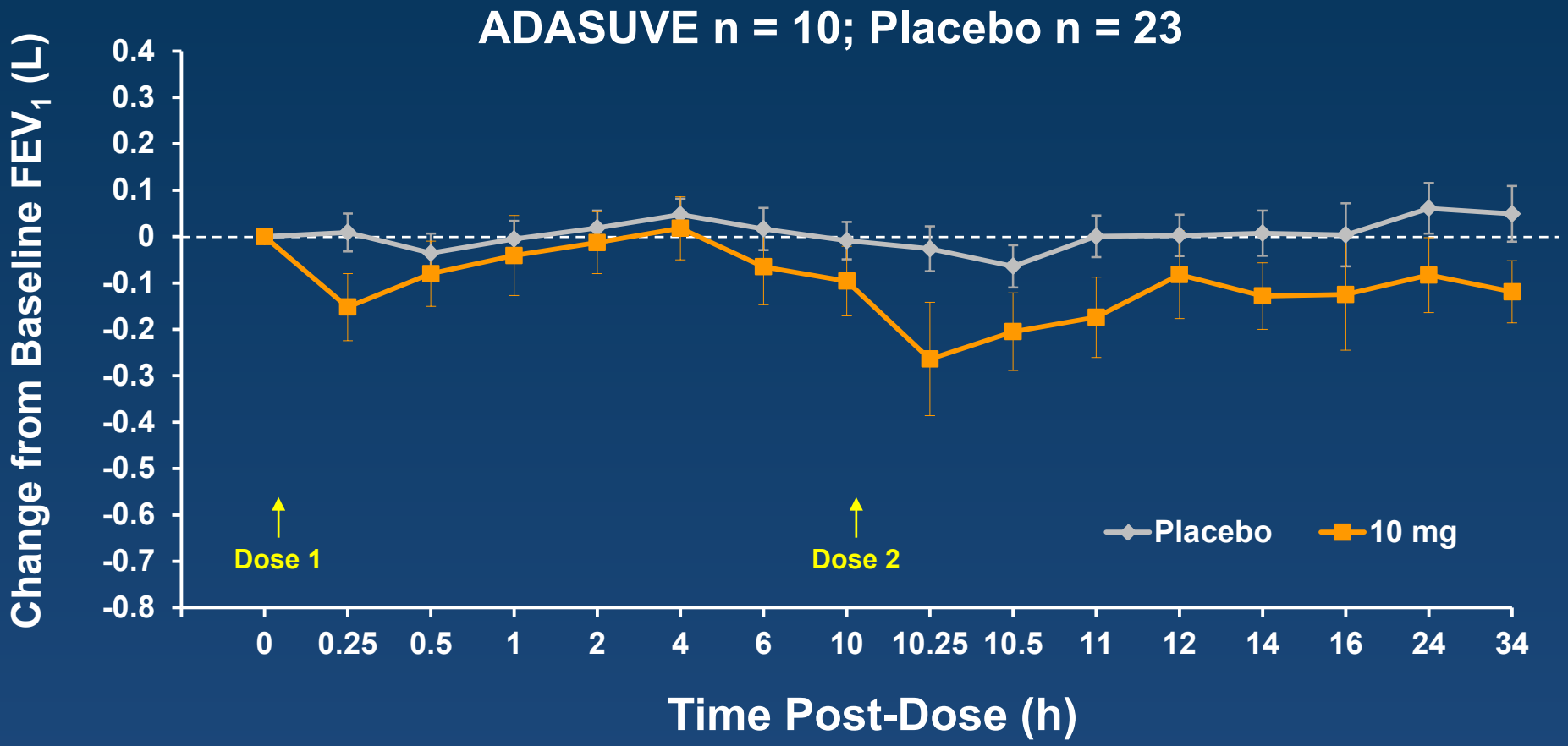
Change in FEV_1 from Baseline Asthma Study



Time (h):	0	0.25	0.5	1	2	4	6	10	10.25	10.5	11	12	14	16	24	34
No. Pbo:	26	26	26	26	25	25	25	25	24	24	21	23	23	23	23	23
No. Active:	26	26	22	22	22	21	20	20	17	12	12	12	12	12	11	10

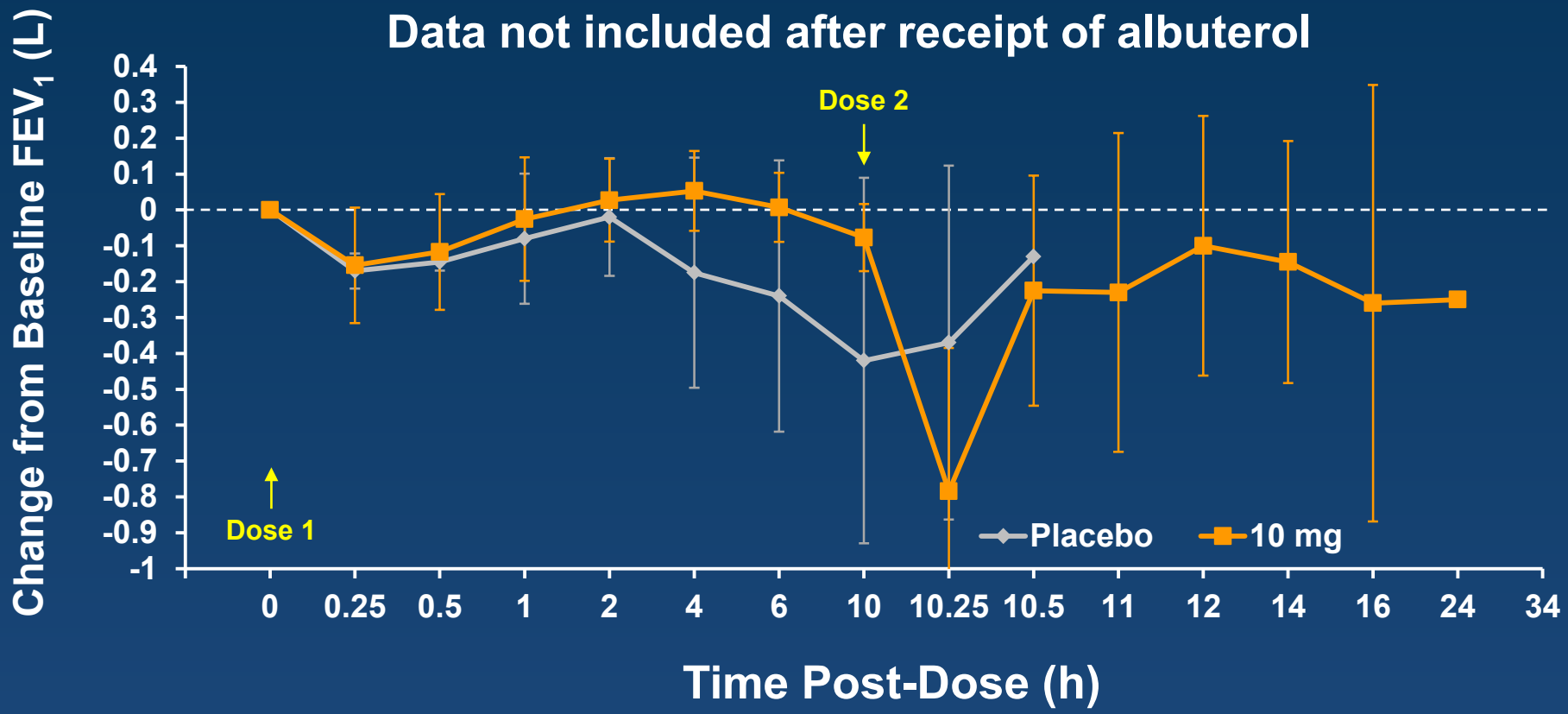
LSmeans and 90% LSmean CI

Change in FEV_1 from Baseline: Subjects Who Did Not Receive Albuterol Asthma Study (Completers)



Means ± 90% CI

Change in FEV_1 from Baseline: Subjects Who Received Rescue Albuterol after Dose 2 Asthma Study



Time (h):	0	0.25	0.5	1	2	4	6	10	10.25	10.5	11	12	14	16	24	34
No. Pbo:	2	2	2	2	2	2	2	2	2	1	-	-	-	-	-	-
No. Active:	7	7	7	7	7	7	7	7	7	2	2	2	2	2	1	-

Means ± 90% CI

Categorical Changes in FEV_1 Asthma Study

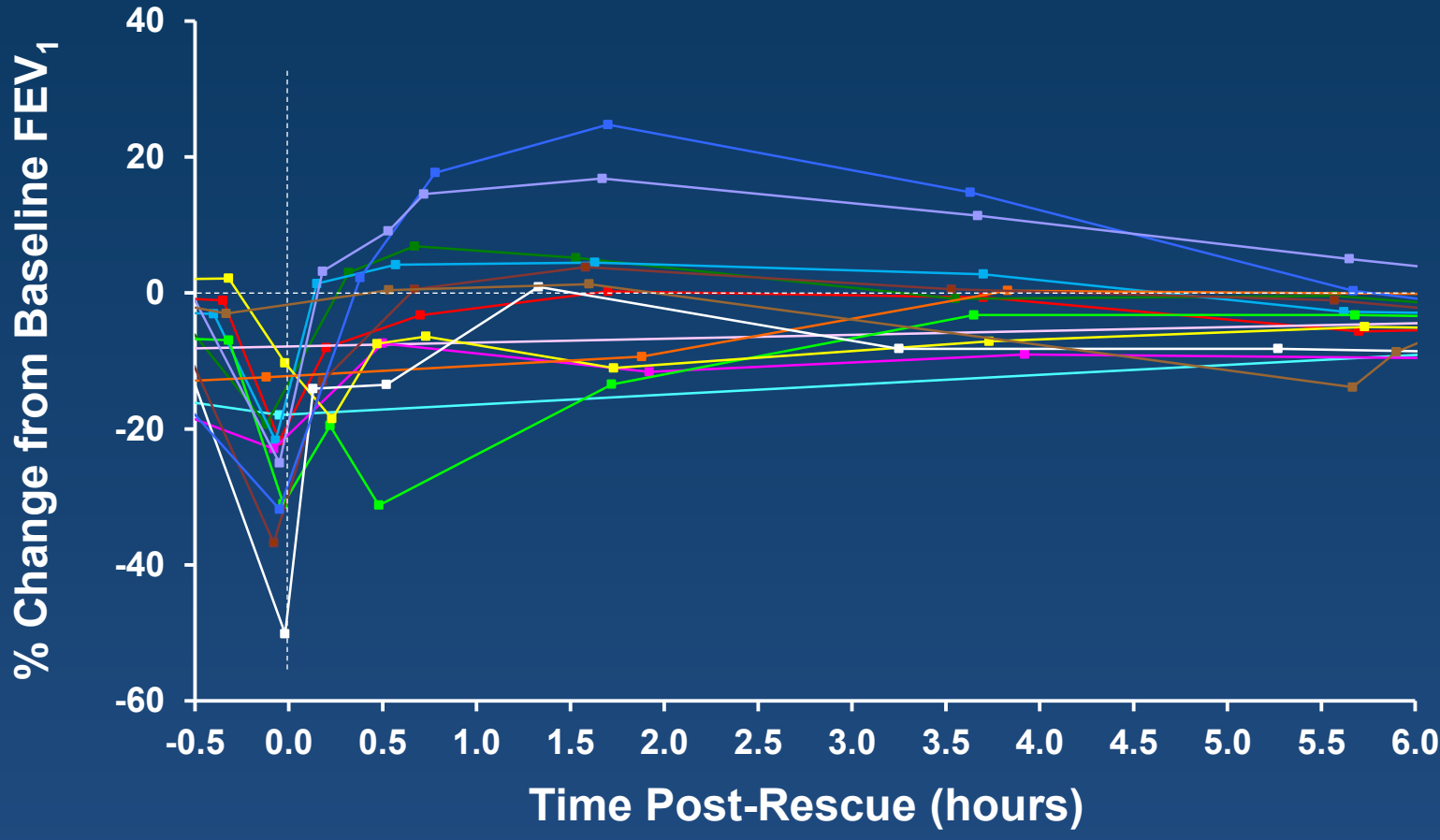
Number of Subjects with Maximum FEV_1 Decrease from Baseline After Either Dose of at Least 10%, 15%, or 20%

Maximum % FEV_1 Decrease*	*Staccato* Placebo (N=26)	ADASUVE (N=26)
≥10%	3 (11.5%)	22 (84.6%)
≥15%	1 (3.8%)	16 (61.5%)
≥20%	1 (3.8%)	11 (42.3%)

* Includes time points through 24 h after Dose 1

FEV_1 Response to Albuterol: ADASUVE Asthma Study

- 14/26 subjects received albuterol (13 for an airway AE)
  - 13/14 subjects required only single doses



Airway AEs
Asthma Study

Incidence of Airway Adverse Events

	Staccato Placebo (N=26)	ADASUVE (N=26)
Any airway AE*	3 (11.5%)	14 (53.8%)

* Includes reports of bronchospasm, dyspnea, wheezing, cough, chest discomfort, throat tightness, and FEV_1 decreased

Airway AEs
Asthma Study

Incidence of Airway Adverse Events

	Staccato Placebo (N=26)	ADASUVE (N=26)
Any airway AE*	3 (11.5%)	14 (53.8%)

Characterization of Airway Adverse Events after ADASUVE

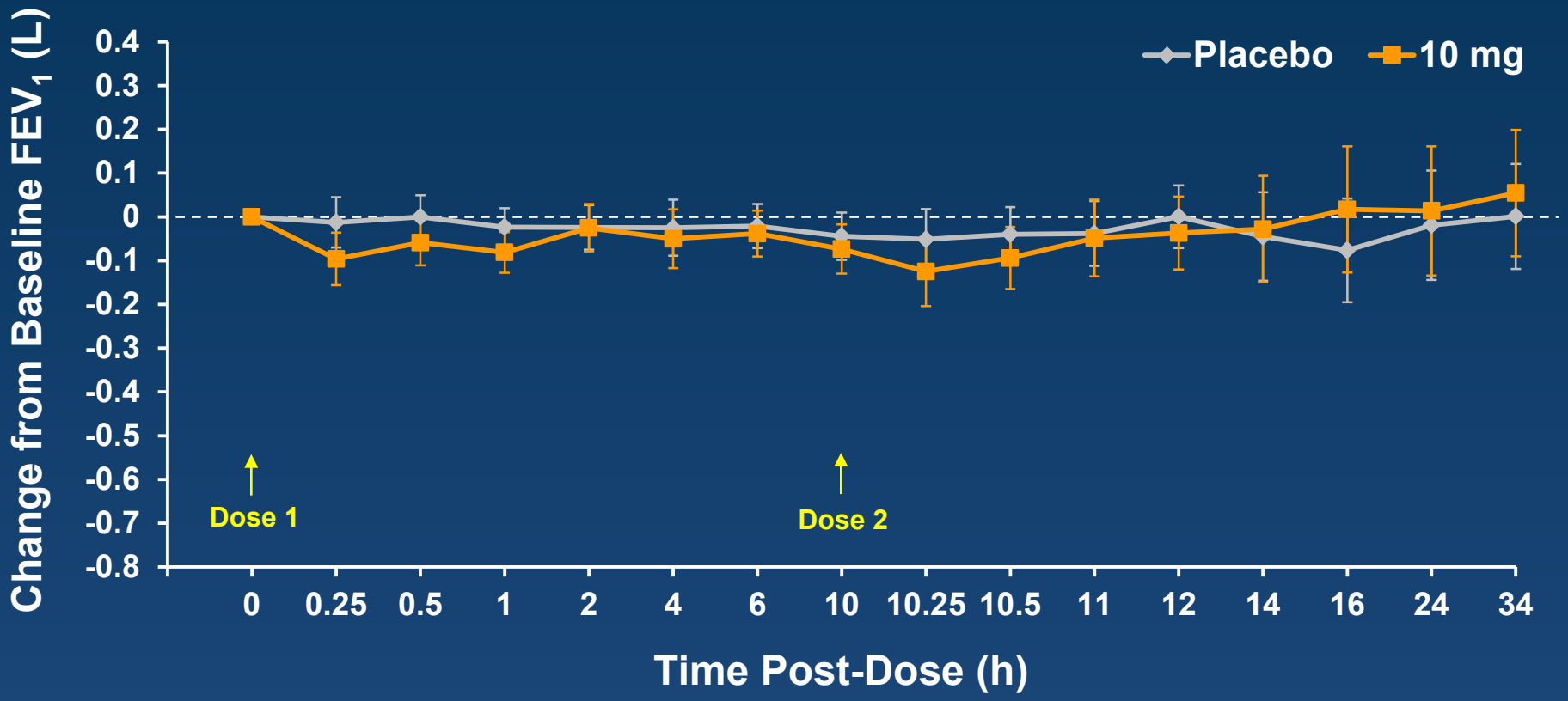
	Asthma Study
Timing	12/14 within 25 min after dosing
Severity	All mild-moderate

* Includes reports of bronchospasm, dyspnea, wheezing, cough, chest discomfort, throat tightness, and FEV_1 decreased

Severity at Screening
COPD Study

	N = 53
COPD severity at screening (GOLD criteria), N (%):	
Mild (FEV_1 ≥80% of predicted and FEV_1/FVC ≤0.7)	6 (11.3%)
Moderate (FEV_1 50% to <80% of predicted)	30 (56.6%)
Severe (FEV_1 30% to <50% of predicted)	17 (32.1%)
Screening post-bronchodilator FEV_1 (% of predicted), median (range)	55.0% (40.0% - 96.0%)

Change in FEV_1 from Baseline COPD Study



Time (h):	0	0.25	0.5	1	2	4	6	10	10.25	10.5	11	12	14	16	24	34
No. Pbo:	27	27	27	27	27	26	25	25	25	25	25	25	25	24	23	23
No. Active:	25	25	24	24	24	24	23	23	19	18	17	18	17	16	16	15

LSmeans and 90% LSmean CI

Categorical Changes in FEV_1 COPD Study

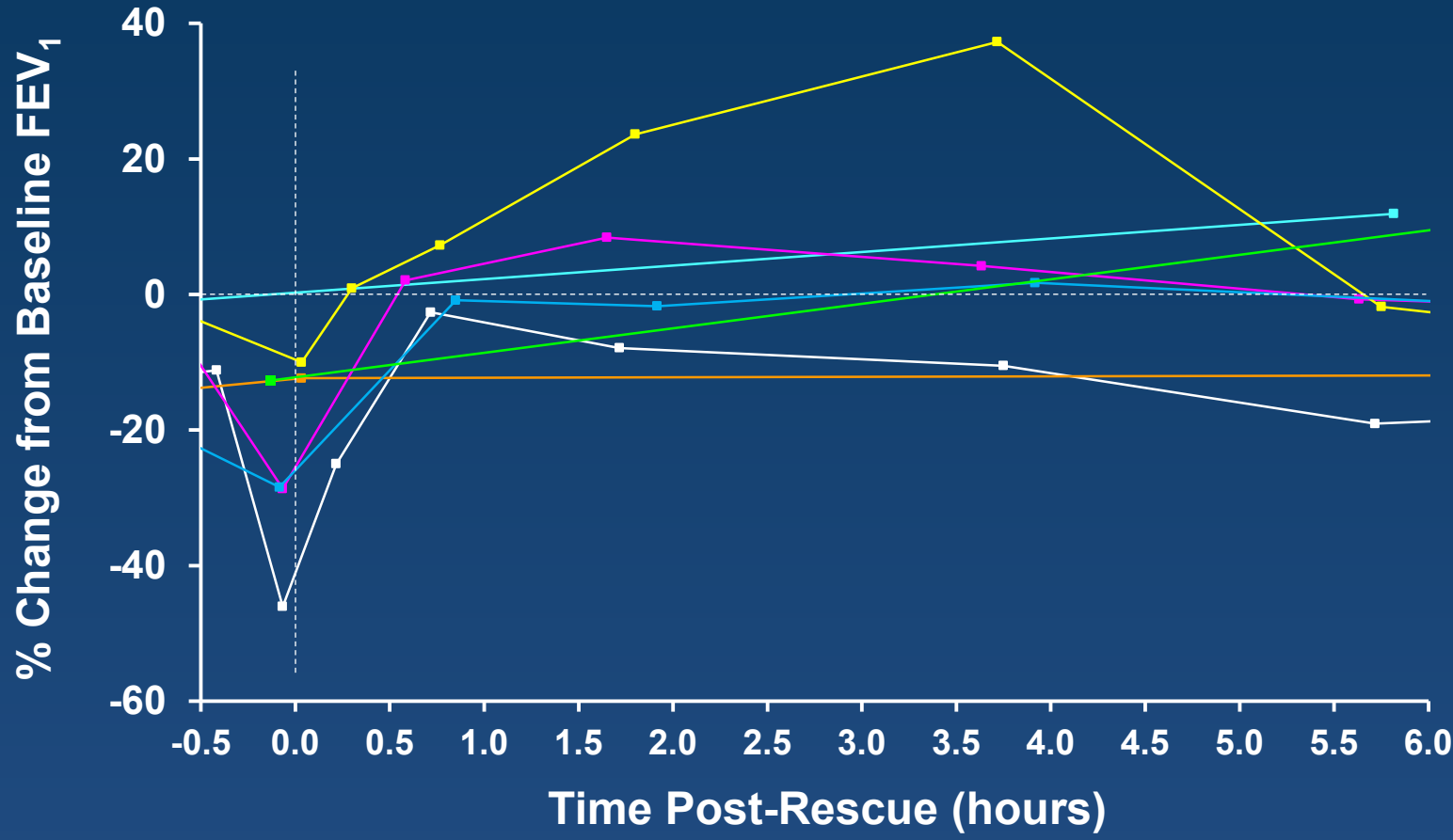
Number of Subjects with Maximum FEV_1 Decrease from Baseline After Either Dose of at Least 10%, 15%, or 20%

Maximum % FEV_1 Decrease*	*Staccato* Placebo (N=27)	ADASUVE (N=25)
≥10%	18 (66.7%)	20 (80.0%)
≥15%	9 (33.3%)	14 (56.0%)
≥20%	3 (11.1%)	10 (40.0%)

* Includes time points through 24 h after Dose 1

FEV_1 Response to Albuterol: ADASUVE COPD Study

- 6/26 subjects received albuterol (3 for an airway AE)
  - All airway AEs treated with single doses



Airway AEs
COPD Study

Incidence of Airway Adverse Events

	Staccato Placebo (N=27)	ADASUVE (N=26)
Any airway AE*	3 (11.1%)	5 (19.2%)

*Includes reports of bronchospasm, dyspnea, wheezing, cough, pulmonary congestion, productive cough, and FEV_1 decreased

Airway AEs
COPD Study

Incidence of Airway Adverse Events

	Staccato Placebo (N=27)	ADASUVE (N=26)
Any airway AE*	3 (11.1%)	5 (19.2%)

Characterization of Airway Adverse Events after ADASUVE

	COPD Study
Timing	4/5 within 25 min after dosing
Severity	All mild-moderate

*Includes reports of bronchospasm, dyspnea, wheezing, cough, pulmonary congestion, productive cough, and FEV_1 decreased

Safety Summary & Conclusions

- In patients with agitation, ADASUVE was generally safe and well tolerated
  - Most of the AEs in agitated patients are known effects of loxapine
- Bronchospasm has been identified as a safety concern
  - Airway adverse events (mild to moderate) were common in subjects with active airways disease
  - Airway adverse events were reliably managed with an inhaled bronchodilator
- There was a quick FEV_1 response to inhaled albuterol
- There was a low risk of bronchospasm in patients without active airways disease
- Bronchospasm was manageable and reversible

Risk Management

James Cassella, PhD

Risk Management Rationale

- The clinical development program has identified that patients with active airways disease are at risk for bronchospasm
  - Bronchospasm is well characterized
  - Resolves with albuterol
- The Risk Management Plan is designed to mitigate the risk of bronchospasm, by:
  - Preventing at-risk patients from getting product
  - Preparing physicians to manage bronchospasm should it occur
- Phase 4 Observational Study
  - Designed to further characterize benefit - risk

Risk Management Framework

- ADASUVE labeling and REMS are designed to mitigate risk of bronchospasm at every step of treating patients with agitation

Exclude patients with active airways disease	→	Screen
Look for bronchospasm post-ADASUVE dosing	→	Observe
Make facility ready to manage bronchospasm if it occurs	→	Manage

Proposed Product Labeling

- Risk of bronchospasm addressed in:
  - Boxed Warning
  - Contraindications statement
  - Warnings / Precautions
  - Contraindication statement on pouch label

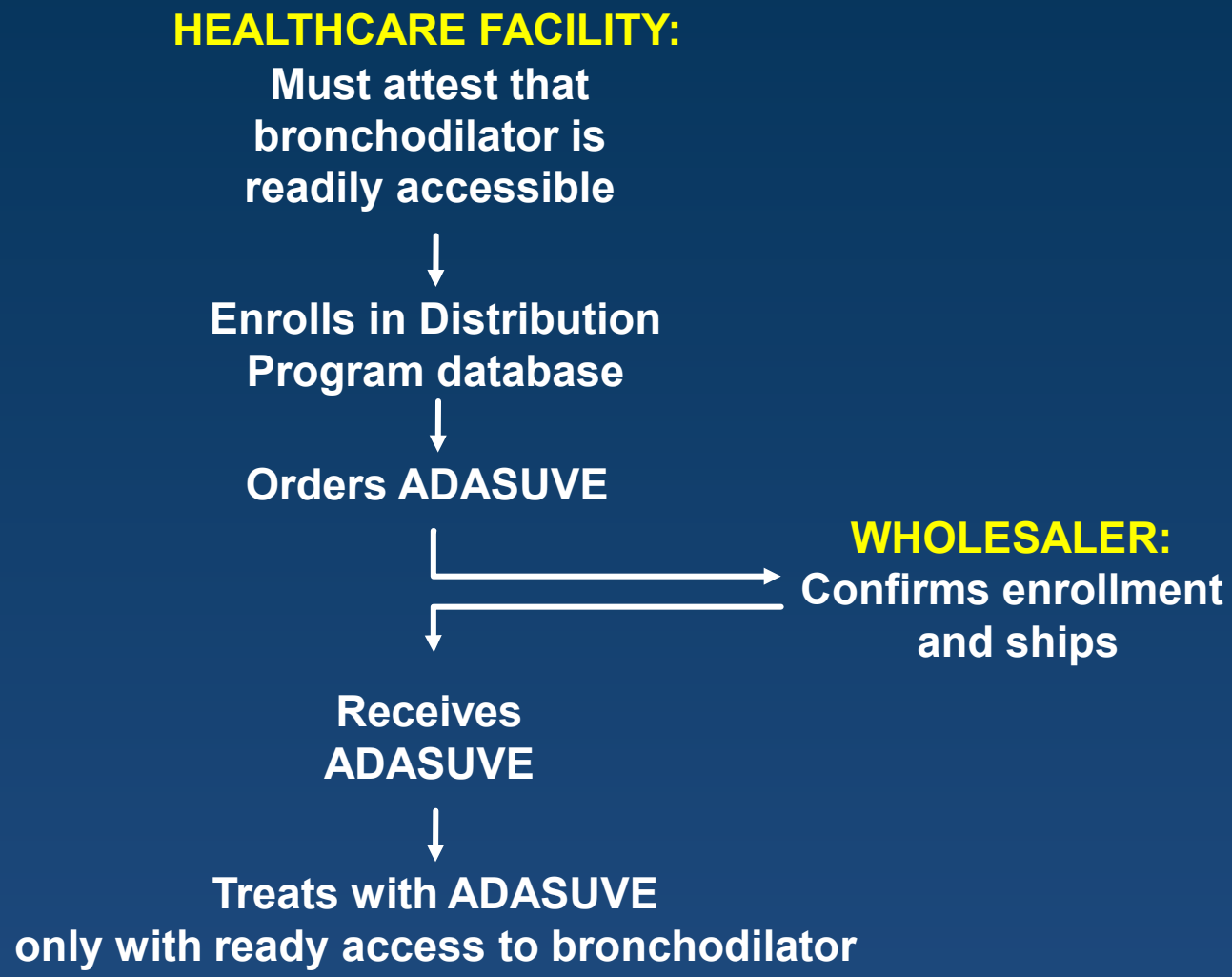
Proposed REMS: Medication Guide

- Attached to each pouch
- Explains risk of bronchospasm
- Instructs patients to tell doctor or nurse if they develop symptoms of bronchospasm
- Supports healthcare professional counseling of patients about the safe use of ADASUVE

Proposed REMS: Communication Plan

- Informs doctors and nurses about how to mitigate the risk of bronchospasm
- Three key communication messages
  - **Select** appropriate patients
  - **Observe** patient after each treatment
  - **Manage** bronchospasm should it occur
- Components:
  - Dear Healthcare Professional Letter
  - Prescriber Brochure
  - ADASUVE Education Program (in-service, online)
  - ADASUVE Safe Use Checklist

Proposed REMS: Distribution to Qualified Facilities



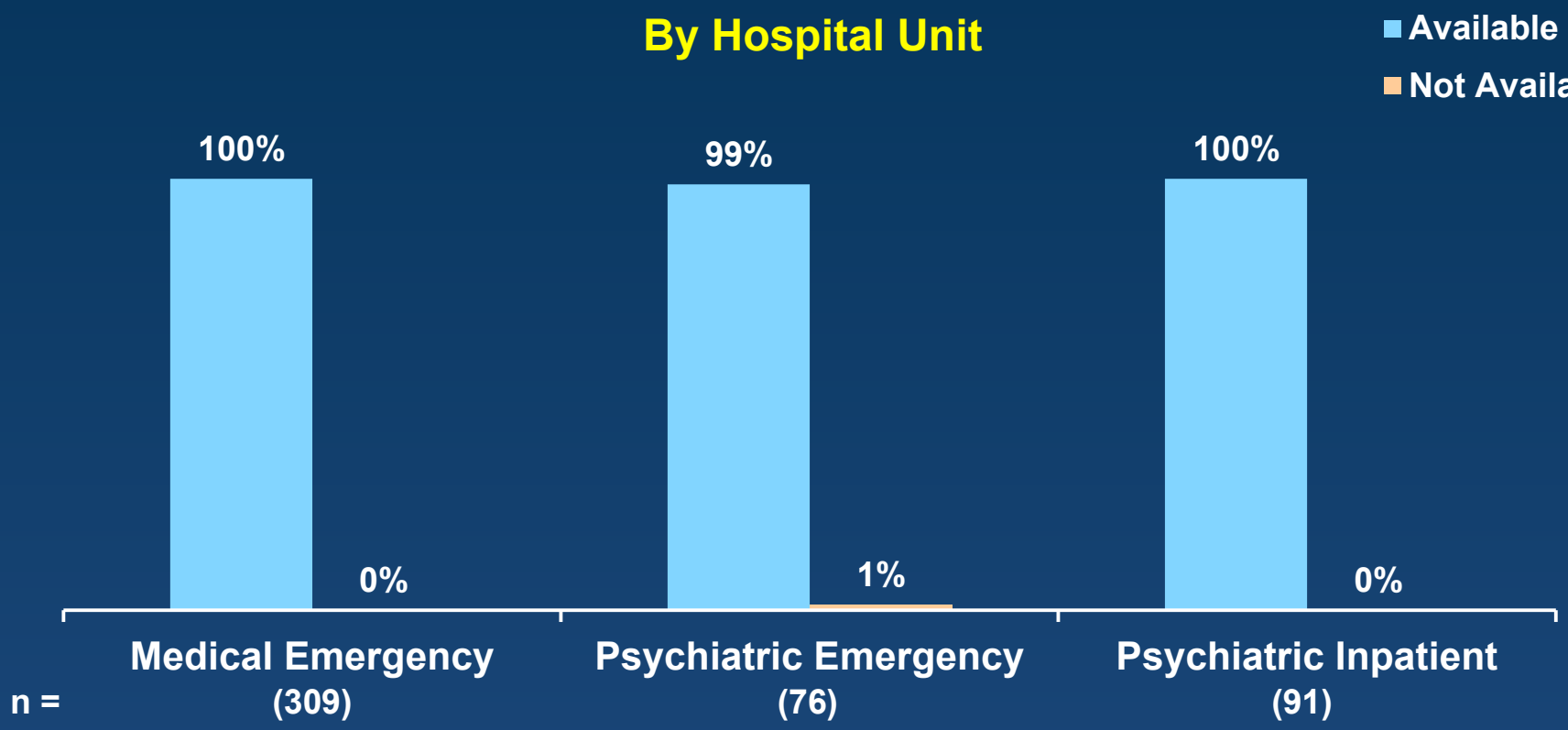
Medical Practice Survey Upon Presentation of Agitated Patient

- Triage procedures surveyed in 3 types of units: Medical Emergency, Psychiatric Emergency, Psychiatric Inpatient
- N=476 web interviews with physicians / nurses
- Results: Medical screening assessments routinely conducted to "medically clear" patients

97 – 99%	Take medical history
91 – 98%	Conduct Physical Exam
80 – 89%	Check for Breathing Problems

Source: National Analysts Worldwide Research Consulting, Jul 2011

Availability of Albuterol in Treatment Settings



- 475 out of 476 units surveyed currently have albuterol available

Q2:Is albuterol available or obtainable in the [emergency department/psychiatric ED/psychiatric unit] at [HOSPITAL FROM s6]?

Source: National Analysts Worldwide Research Consulting, Jul 2011

Standard Observation / Monitoring Practice Survey: Post Agitation Treatment

- Observation and monitoring procedures surveyed in 3 types of units: Medical Emergency, Psychiatric Emergency, Psychiatric Inpatient
- N=195 web interviews with physicians / nurses
- Results: Observation and monitoring procedures routinely conducted after agitation treatment

78 – 88%	Have standard practices for monitoring patients after receiving agitation treatment
91 – 97%	Include respiratory assessments

Source: National Analysts Worldwide Research Consulting, Jul 2011

Risk Management Approach

Key Messages	Labeling	REMS	Implementation
Identify and select appropriate patients	• Boxed Warning • Contraindication • Warnings and Precautions • Contraindication on pouch label	• Medication Guide • Communication Plan	Reinforce standard practice
Observe patients after treatment	• Boxed Warning • Warnings and Precautions	Same as above	Reinforce standard practice
Manage bronchospasm with bronchodilator	• Boxed Warning • Warnings and Precautions	Same as above Plus distribution only to facilities with ready access to bronchodilator (ETASU)	Facility Enrollment and Distribution Program

Proposed Phase 4 Observational Study

- Evaluate safety and efficacy in real-world Emergency Departments
  - 1400 patients in approximately 50 centers
    - Require anti-psychotic (IM or aerosol) and/or IM benzodiazepine treatment
- Outcomes would include:
  - Respiratory AEs
  - Use of short-acting bronchodilator or other medication to treat emergent symptoms
  - Other AEs such as sedation/somnolence, EPS
  - SAEs

Proposed Phase 4 Observational Study
Assessment of Treatment Patterns and Effectiveness

- Baseline PEC scores (ADASUVE compared with other anti-agitation medications)
- Mean change in PEC from baseline to 1 h post-treatment
- Usability of ADASUVE (number refused or unable to use)
- Physician treatment choices for treating agitation in an emergency setting
- Doses of all anti-agitation medications administered (up to 24 h from first dose)
- Physical restraints used
- Security personnel or dedicated staff post-dosing
- Availability of patient medical/medication history and physical examination results prior to treatment

ADASUVE in the Emergency Department

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T_{max} Values for Drugs Used to Treat Agitation

	IM T_{max} (minutes)	Oral T_{max} (hours)
Haloperidol[1]	36	2 - 5
Olanzapine[2]	15 - 45	6
Ziprasidone[3]	60	6 - 8
Aripiprazole[4]	60 - 90	3 - 5
Lorazepam[5]	60 - 90	1 - 6

[1] Goodman and Gilman's, 11th Ed, 2006, [2] Zyprexa Prescribing Information Jun 2011,
[3] Geodon Prescribing Information Dec 2010, [4] Abilify Prescribing Information Feb 2011,
[5] Ativan Prescribing Information , Sep 2010

Time to First Statistically Significant Change from Baseline PEC Scores (Comparator Studies - Schizophrenia)

Study	ADASUVE STUDY 5mg	10mg
004-301	10 min	10 min

Study	IM ABILIFY STUDIES 1mg	5mg	10mg	15mg
CN138012	nt	nt	120 min	nt
CN138050	ns	120 min	45 min	120 min

Study	IM ZYPREXA STUDIES 2.5mg	5mg	7.5mg	10mg
F1D-MC-HGHB	nt	nt	nt	15 min
F1D-MC-HGHV	60 min	30 min	30 min	30 min

nt: not tested in study
ns: not statistically significant (compared with placebo)
Source: Zyprexa, NDA 21-253 Statistical review; Abilify, NDA 21-866 Statistical Review

Time to First Statistically Significant Change from Baseline PEC Scores (Comparator Studies – Bipolar Disorder)

ADASUVE STUDY		
Study	5mg	10mg
004-302	10 min	10 min

IM ABILIFY STUDY		
Study	10mg	15mg
CN138013	90 min	60 min

IM ZYPREXA STUDY	
Study	10mg
F1D-MC-HGHW	30 min

Source: Zyprexa, NDA 21-253 Statistical review; Abilify, NDA 21-866 Statistical Review

PEC Scale Responders (Comparator Studies - Schizophrenia)

Study	Minutes after Dose 1	Placebo	Dose			
			1mg	5mg	10mg	15mg
IM Abilify CN138012	120	42%	nt	nt	57% (p=0.045)	nt
IM Abilify CN138050	60	24%	20% (ns)	30% (ns)	45% (p<0.05)	45% (p<0.05)
	120	36%	38% (ns)	50% (ns)	54% (p<0.05)	55% (ns)

Study	Minutes after Dose 1	Placebo	Dose			
			2.5mg	5mg	7.5mg	10mg
IM Zyprexa F1D-MC-HGHB	120	33.3%	nt	nt	nt	73% (p<0.01)
IM Zyprexa F1D-MC-HGHV	120	20%	50% (p=0.003)	62.6% (p<0.001)	73.9% (p<0.001)	80.4% (p<0.001)

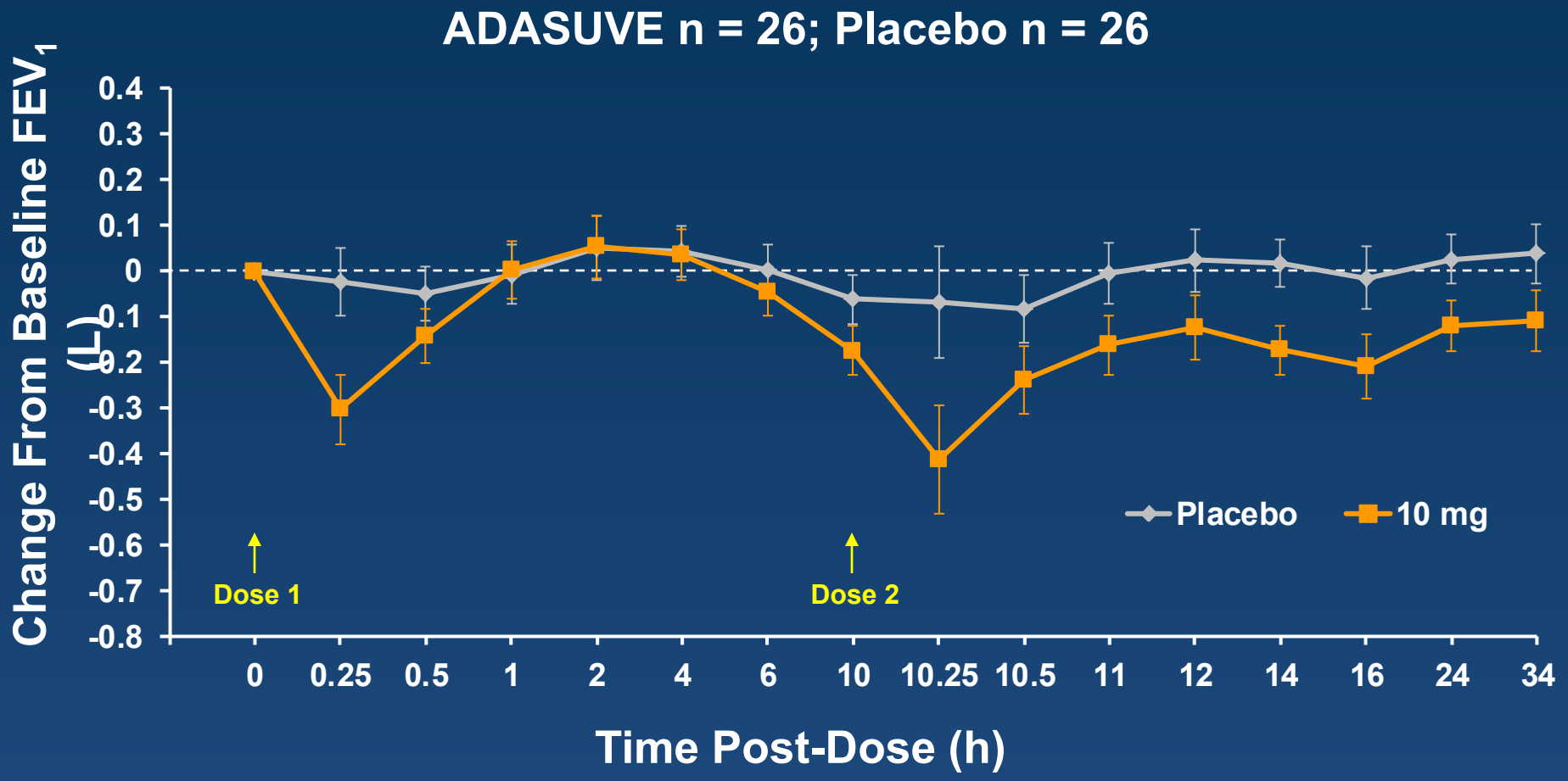
nt=not tested in study

PEC Scale Responders (Comparator Studies - Bipolar Disorder)

Study	Minutes after Dose 1	Placebo	Dose	
			10mg	15mg
IM Abilify CN138013	30	18%	12% (ns)	13% (ns)
	45	26%	37% (ns)	35% (ns)
	60	37%	43% (ns)	48% (ns)
	90	41%	57% (p=0.046)	52% (ns)
	120	37%	69% (p<0.001)	63% (p=0.002)
IM Zyprexa F1D-MC-HGHW	30	28%	50.0%	nt
	120	44%	80.6% (p<0.0001)	nt

nt= not tested in study

FEV_1 Over Time (Asthma Study) (All Data)



LSmeans and 90% LSmean CI

Recovery of FEV_1 in Subjects Who Received Dose 1 Only (Asthma Study) (All Data)